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MAP FOR 'DRUG AND FOOD' IN CANCER NUTRITION

Ugur Gogus

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Specific Nutrition Pathways During Chemotherapy for Patients with Cancer



Dr. Ugur Gogus
Food Science & Technology, Ph.D.

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We have to improve the strenght of chemotherapeutic drugs in cancer treatments. On the other hand, these agents have many serious side effects. Although there has been no diet for the patients with cancer, media and authorities still continue to define a cliche nutrition program, consisting of green leafy vegetables, fish meat, fruits, olive oil.. This cliche nutrition may help to protect the healthy consumers against cancer, but the nutrition program or diet changes when it comes to the consumers with cancer. Such a nutrition program can only be designed by evaluating and analysing the antagonisms and synergisms of the anti-cancer drug administered and the active food compounds in each food. Only after these detailed evaluations, a nutrition program which is specific for only the administered anti-cancer drug can be designed. The book which addressed to more than 2900 studies in cancer nutrition, screened from Science Direct, CrossRef, Google and PubMed databases, is a first to meet this important demand of both oncologists, nurses, dietitians, food scientists and patients with cancer while it is the most detailed review in cancer nutrition, currently. When it will be useful for the mentioned groups, then one of my biggest missions in the world will have been accomplished.

My dear Mom Yaşar, you have always been a motivation for me to perform this study. My pray for you, for my mom and father, will continue as long as I live.

Special thanks to my dear wife and my lifeblood
Fulya and my angel Ayşenur Mert.

My students and close friends; Muzaffer Güneş, Utku Sabah, Ece Ural and Hazal Karakuş, I am so glad to be with you in my life.

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Preface
MAP for 'DRUG and FOOD' in CANCER NUTRITION

Currently, we have neither a nutrition nor a diet program for patients with cancer. Media with its cliché programs and their well known popular academicians and researchers claim the protection from cancer with a fish meat, green leafy vegetable and complex carbohydrate-fiber rich nutrition. Such a nutrition program or diet can only be protective for healthy people, but not necessarily for cancer patients who are prescribed with chemotherapeutic agents and radiation. Therefore, a great demand is exist for a specific design of a nutrition program or diet whose contraindications and interactions with the administered chemotherapeutic agent are determined. On the other hand, clinic nutrition and oncology have reached a much better status than ever before by highlighting the cancerogenic pathways, cancerogenic and anticancerogenic signals and the effects of many bio-active food compounds on these pathways and signals. A brief look at the status of Reactive Oxygen Species (ROS) which are the end products of food combustion during digestion may explain this demand, the aim and scope of the book. Reactive Oxygen Species (ROS) are generated by oxidant enzymes, phagocytic cells and ionizing radiation while their production is induced by a free radical. A free radical is any species which contains one or more unpaired electrons. The unpaired electron makes the free radical more reactive. Superoxide anion ($O_2^{\cdot}$) is the first free radical, formed by the electron transport chain when O_2 picks up a single electron. Other ROS like hydroxyl (OH), perhydroxyl (HO_2) and hydrogen peroxide (H_2O_2) are formed by the superoxide anion ($O_2^{\cdot}$) (Nappi and Vass, 1998). The superoxide anion ($O_2^{\cdot}$) enters into a reaction to form H_2O_2 by the enzyme superoxide dismutase (SOD). H_2O_2 is not reactive enough to cause damage on cell, but it can cross the cell membrane and form highly reactive and thus, very harmful hydroxyl radical (OH) by interacting with metals such as Fe^{2+} and Cu^{+}. The elevated levels of modified bases in DNA like the substitution of CC

to TT (Reid and Loeb 1993), which results in cancer may be due to the large amount of H_2O_2 production and its harmful end product, hydroxyl (OH). Briefly, the free oxygen radical species are concerned as one of the initial and strongest factors that initiate cancer in human (Ames et al. 1993; Poulsen et al. 1998). The formation of the reactive and harmful hydroxyl radical (OH) from harmless H_2O_2, is one of the most critical points that indicates to the role of antioxidants and antioxidant rich foods, especially fruits and vegetables since H_2O_2 can be neutralized by the antioxidant enzymes, catalase and glutathione peroxidase. The protein, catalase, has a 3D structure in its active form and a heme group. The neutralization of ROS starts with the oxidation of Fe (III) to a more oxidized form Fe (IV) in the heme group of catalase, releasing H_2O and oxygen. In the second part of the neutralization with catalase, the second molecule of H_2O_2 is converted back into water by the effect of oxygen while reducing Fe (IV) back to Fe (III). Briefly, catalase breaks down H_2O_2 into water and oxygen, preventing the formation of harmful free radical, hydroxyl (OH) which mutates the DNA plasmid (Khan et al. 2005) (Ahmad et al. 2009; Hussain et al. 2003). On the other hand, glutathione peroxidase catalyzes the harmful and pro-oncogenic hydroxyl radical (OH), yielding GSSG (oxidized glutathione), water and alcohol (Toppo et al. 2009). Thus, any food rich in catalase or glutathione peroxidase may contribute to prevent from cancer. This means that the rich sources, whose rich catalase and/or glutathione contents are determined by the researchers in the following parentheses, such as wheat sprouts (Marsili et al. 2004), potato (Spychalla and Desborough 1990), carrot (Baardseth and Slinde 1983), Onion (Lee et al. 2012), garlic (Perchellet et al. 1986), Broccoli (Davis et al. 2002), Brussels sprouts (Sorensen et al. 2001; Hoelzl et al. 2008), cabbage, sweet potato, daikon (Hossain et al. 2013), pumpkin (Nkosi et al. 2006), Avocado (Mahmoed and Rezq 2013), spinach (Sheptovitsky and Brudviq 1996), may help to prevent from cancer with their anticarcinogenic potential due to their inhibitory effect on H_2O_2 with their rich catalase and glutathione concentrations.

The consumptions of sugar and fat rich foods in excess amounts without control for long periods may result in cancer since ROS can rupture the cell membrane, enter into cell and change the genom. The

damage and mutation in the cell genom by ROS may result in an abnormal cell proliferation. A large amount of data from various researches indicates to the generation of high levels of ROS in cancer cells with a high rate of oxidative stress. Some levels of ROS and the signals from the ROS are used to drive proliferation and tumor progression. The higher levels of ROS and the use of their signals in cell proliferation and tumor progression have already been confirmed (Schumacker 2006; Waris and Ahsan 2006 and Chen et al. 2014). Although ROS are claimed as one of the biggest crucial factors in the progress of various metabolic diseases, aging and cancer, the current data indicates that they may also have a dual effect in cancer. The higher concentrations of ROS in cancer cells, when combined with anti-cancer treatments which cause the generation of ROS, may kill the cancer cells, by increasing the total ROS concentrations and the damage by the ROS on cancer cells, like the damage by the irradiation on Burkitt lymphoma B and epithelial breast cancer cells (Minai et al. 2013), ROS triggered degradation of the polyplex and the release of DNA of the cancer cells (Shim and Xia 2013), the inhibitory effect of the combined use of procarbazine, a monoamine oxidase inhibitor and radiation on lung cancer cells (Berneis et al. 1966; Landgren et al. 1973; Palmer and Kroening 1978), the activation of the oncogene, Ras (a potent cancerogen), as combined with the enzyme, NOX4 (NADPH oxidase 4) and their damage on PDAC (pancreatic ductal adenocarcinoma) cells (Ogrunch et al. 2014) and the damage of the administration of reactive oxygen and reactive nitrogen species (ROS/RNS), generated by atmospheric pressure air plasma, on the cervical cancer HeLa cell (Ahn et al. 2014). One of the apoptotic effects of ROS is via the interaction with the genes which regulate apoptosis (programmed cell death). Rotenone, an anticancer drug which kills the cancer cells by decreasing the antiapoptotic protein, Bcl-2 and increasing the apoptotic protein, Bax while inactivating the antiapoptotic genes, ERK1/2 (serine/threonine kinases) in a ROS dependent manner (Deng et al. 2010; Stanciu et al. 2000; El-Najjar et al. 2010). The apoptosis induced by ROS is not only caused by some of chemotherapeutic drugs, but also some bio-active food compounds such as sulforaphane. The bio-active compound, as one of the most commonly known anti-cancer substances, found in

cruciferous vegetables, alters mitochondrial membrane potential after it induces ROS generation, Bcl-2 and HTERT (Telomerase Reverse Transcriptase which repairs the defects in the chromosoms) (Choi et al. 2008; Meeran et al. 2010). The generation and influx of ROS trigger the proapoptotic protein, Bax, while Bax permeabilizes the outer mitochondrial membrane, releasing the apoptotic proteins, cytochrome c and Caspases, the proapoptotic cystein-dependent aspartate-directed proteases or cysteine-aspartic proteases which result in apoptosis (Hsu et al. 1997; Antonsson et al. 2001; Li et al. 1997). The anticancer drugs whose anticancerogenic effects, due to their inductions on ROS and Caspases, which are determined by their references in the parenthesis are; costunolide (the stem bark of *Magnolia sieboldii*, a sesquiterpene lactone) (Kanno et al. 2008), mitomycin c (Pirnia et al. 2002), cisplatin (Kaushal et al. 2001), garcinol (Pan et al. 2001), brefeldin A (Lee et al. 2013), valinomycin (Abdalah et al. 2006), piceatannol (Kim et al. 2008), kinetin riboside (Dudzik et al. 2011), lipase inhibitor, THL (tetrahydrolipstatin) (Yao et al. 2011), imiquimod (Schon et al. 2003), SC560 (Lampiasi et al. 2006), romidepsin (Hanker et al. 2009), ouabain, digoxin, proscillaridin A (Winnicka et al. 2007), borrelidin (Kawamura et al. 2003), sanguinarine, bortezomib (Larsson et al. 2010) MT-21(Watabe et al. 2000), ionidamine (as combined with radiation) (Miyato et al. 2004), K858 (Nakai et al. 2009), saikosaponin A (a triterpene saponin derived from *Bupleurum falcatum L.*) (Kim and Hong 2011), CIL-102 (Huang et al. 2005) and prodigiosin (Montaner and Perez-Tomas 2002). Briefly, one of the crucial factors responsible for many metabolic diseases, aging and cancer, ROS, have currently been exploited by some of the present anti-cancer drugs to kill cancer cells. Confirmingly, the possibility of the stronger antiproliferative effect of the anti-cancer drug, fenretinide and I3C combination may be the generation of reactive oxygen species by both I3C and fenretinide, increasing the total amount of reactive oxygen species to kill tumor cells more (Hwang et al. 2011; Shimamoto et al. 2011; Bai et al. 2013). Extracellular signal-regulated protein kinases 1 and 2 (ERK 1/2), the members of the mitogen-activated protein kinase super family, are phosphorylated and activated followed by ROS generation while ROS generation induce the proapoptotic enzymes Caspases. Confirmingly,

dexamethasone inhibits the growth of various types of cancer cells by first generating ROS and as a result, phosphorylating ERK1/2, activating caspase-9, -3 and -8 (Park et al. 2013) while it also increases the expression of X-linked inhibitor of apoptosis (XIAP)-associated factor 1 (XAF1) which increases the sensitivity of cancer cells to apoptosis (Plenchette et al. 2007), and induces the translocation of proapoptotic protein, Bax, into mitochondria. Briefly, the latest findings clearly indicate a close and significant link during apoptosis among the proapoptotic proteins Bax, ERK1/2 and Caspases, ROS and XAF1. Such a link which leads to apoptosis may also be the reason for one of the anticancerogenic effects of sulphoraphane (Lee and Lee 2011; Keum et al. 2006; Jo et al. 2014; Yeh and Yen 2005 and Li et al. 2014). The formation of reactive oxygen species (ROS) and the induction of caspase activity have also been determined for many other important bio-active compounds. These are, resveratrol, by an increase in cleavage of caspase-8 and caspase-3, in HT-29 and COLO 201 human colon, human U937 leukemic monocyte lymphoma cells, NSCLC (lung cancer), C7H2 (lymphoblastic leukemia), HCT (human colon carcinoma) and SGC790 (human gastric) cancer cells (Miki et al. 2012; Juan et al. 2008; Azmi et al. 2006; Guha et al. 2011; Luo et al. 2013; Tinhofer et al. 2001; Heiss et al. 2007; Wang et al. 2012 and Choi et al. 2009), EGCG (Satoh et al. 2013; Ranzato et al. 2012; Lu et al. 2013), kaempferol (Lee et al. 2014; Halimah et al. 2015 and Luo et al. 2010) genistein (Kim et al. 2013; Niu et al. 2011; Granado-Serrano et al. 2006; Liang et al. 2011), quercetin (Canada et al. 1990; Gaspar et al. 1994), lycopene (Krishnamoorthy et al. 2013; Palozza et al. 2011; Kumavat and Chaudhari 2013; Kim and Kim 2015; Zou et al. 2013), apigenin (Torkin et al. 2005), vitamin C (Chen et al. 2005) and amygdalin (Chang et al. 2006). For all these reasons, if the patient with cancer is prescribed with one or some of the chemotherapeutic agents referred above, then only a specific diet rich in I3C, sulforaphane, resveratrol, EGCG, kaempferol, genistein, quercetin, lycopene, apigenin, vitamin C (ascorbic acid) and amygdalin can be advised. But ROS is not the only pathway in cancer formation and progress. There are many other complex ones such as; p53, Akt, IL6, VEGF, IL8, STAT3, Erbb2, GRP78, COX-2, p38, FOXO3, ERalpha, HO-1, BRCA1, Bcl, CDK, Nf-kB, Hedgehog, iNOS, Hsp90, Cdc25,

IGF-1, MAPK/ERK, PRDX3, AR, Alt, Nrf2, Notch, p38/MAPK, B-catenin, Keap/Nrf25, TNF, Bim, CHOP, MMPs, SOD2, B-catenin/ Wnt, p21, p57, G6PDH, p450/CYP, CDC25A, Bax, NO, Hsp90. The most important point here is to be able to know the effects of each of the special bio-active food compounds in foods on these signals, enzymes and pathways. Only after the effects of each bio-active food compound and the chemotherapeutic agent administered are determined, then the contraindicated foods and their bio-active compounds should have been eliminated while the foods with their bio-active compounds and the chemotherapeutic agents which are in synergism between them and between the mentioned enzymes, signals and pathways should have been included to the anti-cancer diet. Briefly, the creation of a specific anti-cancer nutrition program is not so easy while it requires to determine the effects of each food, bio-active food compound and chemotherapeutic agent on the mentioned signals, enzymes and pathways. That is why I have worked too hard, a work including 13 years, night and day, using more than 2900 studies from 1986. My biggest aim in the book is to address the mentioned difficult nutrition design, specific to chemotherapeutic agent, administered particularly for patients with cancer, their families, oncology departments and their kitchens, nurses in oncology departments, oncologists and pharmacists.

'Cancer and food relation' is the only one of the relations about cancer, while it is the most common and important one!

Cancer is one of the initial most common diseases which human being faces with presently while it has got the second mortality (death rate) after cardiovascular diseases. There are 200 different types of cancer and there is not only single factor in cancer formation since many or several factors may be involved. Thus, cancer may be defined as a multifactorial disease. We know tobacco smoke well since it is one of the important causative agents for the formation of lung cancer. On the other hand, overexposuring to sun light may cause melanoma (skin cancer). Tobacco may not cause skin cancer while overexposure to sunlight may not cause lung cancer. Many of the cancer types have got their own causative agents.

Although there are many substances which may cause cancer, these substances which are called as carcinogens, are not the only factors as I indicated above. There are many persons which are free of cancer all through their life span although they consume too much sugar or sugar rich foods and use tobacco. But, we face with a reality that although there are many factors in cancer formation and foods are not the only group which causes cancer, knowing the carcinogens and foods with higher risk of cancer, is always deathly important for us to be prevented from cancer in our daily life.

One of the carcinogenic groups is the causative agents of infections while these agents often appear as bacteria or virus. On the other hand, environmental substances such as asbestos with many others, some drugs which suppress immune system, some foods such as red meat and its products, fatty milk and dairy products, fried and processed products and sugar rich food products are the other factors which may increase the risk of cancer and they will be analysed in the book with many of their details. Among these factors, especially organ transplants and chronic infections can stimulate cells and cause continued cell divisions. During these cell divisions, the nucleus which contains genetic material,

is more likely to face with a carcinogen and thus many genetic faults which may lead to cancer can form during these divisions.

Why did I make an entrance to the book by explaining the initial causes of cancer.? Some of you may want to know its reason while reading these lines. I only wanted to classify the causative factors of cancer from foods to chronic infections, from drugs to organ transplants. I wanted to show that cancer risk is not only caused by Ford, but may also be caused by environmental factors, genetic factors, infections and drugs. Carcinogenic foods can only be referred as the only one among many carcinogenic factors while several or many of these factors should come together to be able to form cancer. For all these reasons, we can not use definite terms about some foods or food products and make them as the only responsible factors and culprits in the risk and progress of cancer. But, foods are important since there are actually healthy foods and foods with lower risk in increasing cancer risk while there are some harmful foods which may be carcinogenic or which increase the risk and progress of cancer.

Drug may be defined as the substances which cause metabolic changes in body. Food is directly taken to metabolic pathways, used in biochemical reactions to yield energy or used in bone, hormon, blood, cell production and repairment while some of them are the structural components of bone, skeleton, blood and hormones. Drug and food, both are utilized by metabolism and then cause metabolic changes. The difference appears at this point that drug is administered only in case of disease and disorder, whereas we consume food all through the day and life. It is obvious that the effect of foods on our body is much more than the effect of drugs on our body since the administration of foods is much longer in time than the administration time of drugs in a life span. Every drug, as long as they are perfectly selected in the right metabolism, for the right disease, has got beneficial effect which may cure the concerned disease and disorder but all of them have got intense or negligible side effects on our body as well. Similarly, foods have got beneficial effects since we use some of them as our fuel, like carbohydrates, fats, oils and proteins as the structural components of our body. But, each food causes an adverse and harmful effect in our body while making these vital functions. The most important detail at this point is that, some

group of foods or some foods have got less harmful and adverse effects in some conditions, in some diseases and disorders while some others have got more adverse and harmful effects in the same conditions or opposite may happen. Briefly, the foods which should be consumed in some diseases and disorders always change. One or some group of foods may have got more beneficial effects and less harmful effects in some diseases and disorders while one or some groups of foods may have, conversely, more harmful effects and less beneficial effects in the same diseases or disorders. In conclusion, each disease and disorder has got its own nutrition program and its own list of foods.

Why do all foods have less or high adverse and harmful effects on our body while each food has vitaly important function for living? The answer is 'Oxidation', the most important biochemical reaction of the universe, since it is the only energy production pathway which produces energy from food components; fats, oils and carbohydrates. We utilize this energy in all types of our metabolic functions from walking to swimming, from thinking to dreaming. All body functions such as the contraction and relaxation of muscles, heart and blood vessels can only be possible by using this energy. Let me explain this energy production in more detail to be able to understand its important relation with the foods.

We consume fats, oils and carbohydrates by the means of foods. They are first decomposed into smaller fragments in mouth by the effect of saliva and the enzyme, pityalin, which digests starch. The foods pass through oesophagus and then comes into the cavity of stomach and are digested more by the effect of strong acidity (pH 2.3-2.4) in stomach. Finally, the digested carbohydrates, fats, oils and proteins reach into intestines for a further digestion since they are not small enough to be absorbed and transferred into blood through the mucosa cells of intestines. As a result, the special protein structures which are called as enzymes, digest them and decompose them into the smallest structural components. Fats and oils are digested into their smallest structural components which are called as 3 value alcohol, glycerol and free saturated and unsaturated fatty acids, proteins are converted into amino acids and finally carbohydrates are digested as free simple sugars. Free fatty acids, simple sugars and amino acids are the smallest and digested

structural components of fats, oils, carbohydrates and proteins. They are small enough in diameter size to be absorbed and transferred into blood through the mucosa of intestines after all these processes by the effect of enzymes and stomach acidity. The free amino acids, free fatty acids and simple sugars, the smallest and digested end products of complex carbohydrates, proteins and lipids (fats: the solid and animal origin lipids and oils: the liquid and plant origin lipids) are now ready to be absorbed by the mucosa of intestines. They are absorbed through the wall of intestines and transferred into blood. These smallest substances which are the smallest components of complex nutrients reach into each cell in body and utilized by these cells for many metabolic activities, from bone and cartilage formation to hormone and blood production. The wounded cells are repaired by the digested protein compounds, amino acids, while free fatty acids and simple sugars as the end products of complex sugars, fats and oils yield energy. The production of energy from fatty acids of oils and fats and sugars of carbohydrates is the most important one since we utilize all kinds of metabolic reactions and activities by using this energy which is also called as 'kalorie'. The most important reaction of universe, the kalorie production for living, is regulated by some special enyzmes which are the special protein structures. For the mentioned kalorie production, oxygen is inhaled and absorbed through lungs and transferred into blood and reaches into each cell by the means of blood circulation. First, oxygen in the cell combusts free sugars, especially glucose and fructose, and then free fatty acids. The reaction, the combustion of these digestive nutrients in each cell to give energy (kalorie) which are regulated by enzymes is called as 'oxidation' and is the most important biochemical reaction. It is the only reaction which gives energy to all living creatures in universe. Unfortunately, energy is not the only end product which are produced during oxidation.

We need oxidation for living since we need energy and oxidation as the most important reaction in our body because it yields the energy we need. Cardiac pumb in every second, the peristaltic movements of bowel, swimming, walking, thinking, driving, briefly all kinds of metabolic activities are utilized by using this energy. But as I have indicated above, the energy is not the only end product of oxidation, but also free toxic peroxy radical compounds form during oxidation. 'Free

toxic radical compounds' as it can be understood from the term 'toxic' are harmful substances. They are responsible for the formation of all kinds of metabolic diseases and disorders from cancer to diabet, from cardiovascular diseases and disorders such as hypertension, cardiac spasm to stroke unless the level of oxidation is taken under control.

What did I mean when I indicate that free toxic radical compounds may be responsible for the formation of all kinds of metabolic diseases and disorders unless oxidation is taken under control.? Excess level of oxidation, other words, oxidative stress, means the excess amount of energy production by the excess amount of fatty acid and sugar combustion by oxygen. Thus, the main problem here is very obvious that too much sugar and fat rich food consumptions cause directly a high level of oxidation since the combustion of the greater amounts of the mentioned foods yield greater amounts of energy but also greater amounts of free toxic peroxy radicals. You may feel you energetic because of the high rate of oxidation and a greater level of oxidative stress. Eating fat, oil and sugar rich foods may satisfy you since they are much more delicious but also they are energy giving foods and you feel yourself very energetic and satisfied by eating such foods. But, a great problem appears. What about the harmful effects of free toxic radical compounds which are always produced in greater amounts of carbo and fat rich food nutrition?

Excess amounts of free toxic radicals can accumulate around cell membranes and make a mechanical pressure against the wall of the cell. As long as they are not in excess amounts, the defect may not rupture the cell membrane, but these types of cells are wounded cells. The increase in the production of free toxic peroxy radical compounds directly increases the amount of such wounded cells. The greater amount of wounded cells in liver tissue is the main cause of liver failure while the increase in the wounded kidney cells is one of the initial causes of renal failure. Similarly, free toxic radical compounds can wound the membranes of neurons (nerve cells) and brain cells which may be the reason for various neurologic diseases and disorders from Alzheimer to Parkinson and manic depression. Wounded skin cells are the reason for the wrinkles on skin while the increase in the wounded cells of cardiac tissue is responsible for heart failure. The damage given by free

toxic radicals to the surface cells on the mucosa of stomach may cause great defects on mucosa of stomach surface which may be progressive by the effect of stomach acid. This wound is called as 'ulcer'. If the inflammation is on a larger area on stomach surface, the disease is called as 'gastritis'. One of the most harmful effects of free toxic peroxy radical compounds is on cardiovascular system that these harmful compounds accumulate inside the surface of the vessel walls which supply blood into cardiac tissue. Such vessels are called as coronary vessels since they supply blood to cardiac tissue. The accumulation of harmful free toxic peroxy radical compounds may decrease the dimater size of these vessels too much that sufficient amounts of blood can not pass through such calcified vessels which may result in 'cardiac failure' or 'cardiac spasm'. The calcification, the accumulation of free toxic peroxy radical compounds on the wall of vessels and the decrease in diameter size of blood vessels, is called as 'atherosclerosis'. The calcified, otherwords, atherosclerotic vessels, can not circulate enough volume of blood into the tissues because of the decrease in diameter size. Blood can not pass and begins to slow in these calcified regions of vessels and applies a mechanical pressure onto the wall of vessels which is called as 'hypertension' (the increased pressure applied by blood onto the wall of vessel). Also, there is always a risk for the coagulation of the accumulated blood in such calcified cavities. The blood coagulation may partially or completely close the cavitity of vessel which is called as 'thrombosis'. Sometimes, the small fragments, departicipated from thrombose, can reach further parts of vessels and tissues by the means of blood circulation and can cause secondary thrombose formation which is called as 'emboly'. Depending on the severity of the tissue and region which can not supply enough blood because of thrombosis or emboly, the result may be severe and may even be fatal. Finally, the excess of free toxic radical compounds may be converted into sugar and can increase the blood sugar concentration. Normal blood sugar concentration should remain between 70-110 and max. 140 mg/mL. When the limits are exceeded, the water from inside of cell begins to diffuse out to be able to decrease the increased blood sugar concentration to turn it back to normal and thus, these cells become deprived of water and die. The disease is called as 'diabetus mellitus (diabet)'. In conclusion, excess

amount of free toxic radical formation in body is the reason from obesity to hypertension, from stroke to emboly, thrombosis, gastritis, ulcer, diabet and many other metabolic diseases and disorders.

Another important disease which forms due to the increased production of free toxic peroxy radicals is cancer. The consumptions of sugar and fat rich foods in excess amounts without control for long periods, may result in cancer since excess of these harmful compounds can rupture the cell membrane, enter into cell and change the genom of cell. The damage and mutation in the cell genom by free toxic peroxy radical compounds results in an abnormal cell proliferation. Therefore, the protection against cancer should begin by decreasing sugar, fat and oil consumption. We all should be conscious that this type of nutrition may decrease the oxidative stress in body which means the decrease in free toxic radical production as well. So, the cell membranes and the DNA, the genom of each cell, can be protected against these harmful compounds. We, the consumers, should be conscious that, not only because of physical appearance and obesity risk, but more importantly, against the risk of harmful free toxic peroxy radicals, we should avoid from the sugar, fat and oil rich food comsumptions and restrict the consumptions of fat, oil and sugar rich foods and processed foods.

The details given above about the harmful free toxic peroxy radical compounds and energy production seem complex since one of the end producsts, energy, is a must for our living while the other one, toxic radicals, are harmful and responsible for aging and all kinds of metabolic diseases and disorders. Can we stop the production of free toxic radicals.? Of course not. Because, the reaction, oxidation, is the only biochemical reaction which yields energy and it is the only reaction to produce energy. Briefly, we will continue to produce free toxic radical compounds and be suffered with aging and many metabolic diseases and disorders including cancer, while we get older because of free toxic radical compounds.

If we can not stop the free toxic radical production because it is the only energy producing reaction, is there any other way to reduce the prodution rate of these harmful compounds.? Otherwords, is there something we can do by the means of our nutrition and foods, to be able to protect us from various metabolic diseases and disorders including

cancer due to free toxic radicals? The answer includes several foods and food components. One of them which comes at the top of the list is 'antioxidants'.

Antioxidant rich food consumption is the most important way to reduce oxidative stress, free toxic peroxy radical production and prevent from cancer by limiting the excess amount of free toxic radical compounds. Antioxidants are very similar in chemical structure with fatty acids. They replace themselves with fatty acids by using this similarity in their chemical structure and are combusted by oxygen, instead of fatty acids. But, their combustion by oxygen, opposite to free fatty acids, does not yield energy or free toxic peroxy radical. Therefore, the increase in antioxidant rich food consumption is an important and effective way to reduce free toxic peroxy radical. We, the consumer, should never forget that, the reduction of oxidative stress and free toxic peroxy radical production can also prevent from cancer, since the risk of free toxic radical damage on DNA can be reduced by the decrease in their amounts by the means of the rich antioxidant food consumptions. Another group of anticancer agents which are exist in foods is isoflavones. Many scientists define them as a group of vitamins, rather than a different group. Their effect mechanism is the same that they are also similar in their chemical structure and they are combusted by oxygen instead of fatty acids since their chemical structure is very similar to fatty acids and they do not yield free toxic radical followed by the combustion reaction.

The richest antioxidant foods may be classified as in two groups. There is always an easy way to remember them during marketing. If the food is in dark red, yellow, green colors and if the food is sourish in taste, you can use them as antioxidant rich foods. Many people all over the world tend to use the tablets of antioxidants rather than in their native form. All scientific findings claim the same that, an antioxidant can show its antioxidant effect best as in its natural food form. This may probably be due to the separation of the concerned antioxidants during the process of antioxidant supplements. Antioxidants are properly absorbed and transferred into blood if they are together with fats, proteins, carbohydrates. If they are separated from their neighbouring nutrients, their digestion degree decreases. Briefly, the antioxidant rich

foods should always be preferred rather than use antioxidant tablets. But, it is never a fixed rule. Sometimes body requirements may be different and may need special doses of antioxidants. If you are a person who is suffered with osteoporosis (the liability of bones to fractures because of calcium deficiency), calcium tablets, in addition to regular sport and exercise with regular consumption of calcium rich foods such as milk, dairy products, dark green leafy vegetables, soy and soy products may help to lessen the severtity of osteoporosis and slow its progress. The same example may be given for a person suffered with anemia may benefit from vitamin tablets of vitamins; C, B12, folat and folic acid to maximize the beneficial effect of medical treatment, in addition to B12, B complex, C, folat and folic acid rich food products. But, it should always be remembered that B and C vitamins are water soluble vitamins and antioxidants. Even excess amounts of them can be excreted out of body as in the form of urine and faeces. On the other hand, vitamins A, D, E and K are fat soluble vitamins and they can not be excreted by the means of urine and faeces, instead, they can accumulate in blood in greater amounts. Kidney and liver produces fat to be able to disolve and eliminate the excess amounts of these vitamins. The result is the fattening of liver and kidney. Without the control and preventive actions, the fattening of both organs may be too severe and even may cause cancer risk in the long run. For all these reasons, the tablet uses of vitamins A, D, E and K should be avoided and foods rich in these antioxidants should be preffered instead of their tablet forms.

Does oxidant or antioxidant food destroy cancer: A large amount of data from various researches indicates to the generation of high levels ROS of cancer cells with a high rate of oxidative stress. Some levels of ROS and the signals from the ROS are used to drive proliferation and tumor progression. Briefly, having higher levels of ROS and the use of their signals in cell proliferation and tumor progression has already been confirmed by a huge amount of data (Schumacker 2006; Waris and Ahsan 2006 and Chen et al. 2014).

The mentioned higher concentrations of reactive oxygen species in cancer cells, when combined with therapeutic applications which cause the generation of reactive oxygen species, briefly, the very excessive amounts of the radicals may specifically kill the cancer cells, like in

the examples of; the damage by the irradiation on Burkitt lymphoma B and epithelial breast cancer cells (Minai et al. 2013), ROS triggered degradation of the polyplex and the release of DNA of the cancer cells (Shim and Xia 2013), the inhibitory effect of the combined use of procarbazine, a monoamine oxidase inhibitor on lung cancer cells (Berneis et al. 1966; Landgren et al. 1973; Palmer and Kroening 1978), the activation of the gene, oncogene, which is a potent cancerogen, as combined with NOX4 (NADPH oxidase 4) and their damage on PDAC (pancreatic ductal adenocarcinoma) cells (Ogrunch et al. 2014) and the damage of the administration of reactive oxygen and reactive nitrogen species (ROS/RNS), generated by atmospheric pressure air plasma on the cervical cancer HeLa cell (Ahn et al. 2014).

How does the ROS generation induce apoptosis in cancer cells

The findings from a limited number of research suggest that ROS cause apoptosis in cancer cells by interacting with the genes which regulate apoptosis (programmed cell death). An anticancer drug which kills the cancer cells by increasing ROS, rotenone, activates ERK1/2, the genes which are also called serine/threonine kinases. Normally, the genes are antiapoptotic, but the persistent activation of ERK1/2 is asociated with glutamate-induced oxidative toxicity while promoting low potassium-induced neuronal degenaration through membrane damage as being independently of caspase-3 (Stanciu et al. 2000).

Rotenone also cause apoptosis by activating JUN, a protein kinase, and MAPK8 (Mitogen Activated Protein Kinase 8), both of whose apoptotic or proliferative effects depend on the type of stimuli and type of the cancer cells (El-Najjar et al. 2010).

One of the most commonly known anti-cancer substances found in cruciferous vegetables, sulforaphane, first, causes ROS generation and increases the concentrations of ROS. Then, the mitochondrial membrane potential is altered by the ROS while the increase of ROS activates the apoptotic protein, Bcl-2, which also results in apoptosis and triggers of the activation of HTERT (Telomerase Reverse Transcriptase) which repairs the defects in the chromosoms (Choi et al. 2008; Meeran et al. 2010). Briefly, the apoptotic effect of sulforaphane forms by the alteration of the mitochondrial membrane potential due to the ROS generation and then, the activation of the expression of the apoptotic protein, Bcl-2, by ROS.

It becomes clear that, ROS have got dual action in cancer. The level of them should be kept under control to be able to avoid from diseases, disorders and unhealthy aging in healthy individuals, while the same ROS, in individuals with cancer, may be a therapeutic approach.

Factors for Cancer

Proteins, the nutrients which enter into the structure of enzymes that regulate the metabolic reactions in body from blood production to digestion, body lenght and muscle power are in the first priority among other nutrients, lipids (fats and oils) and carbohydrates. Lipids and carbohdrates are also important nutrients since they are the fuel of our body and structural components of our cells. But the superiority of proteins takes its origin from their different functions, all of which are very important for metabolism. Blood, nerve, vessels, hair, joints, bones and tissues would never be repaired, the cells of the mentioned tissues would never be proliferated if proteins had not existed. These nutrients, proteins, may be classified in two groups according to their origin; animal origin proteins and plant origin proteins. When they are compared from the point of nutritious value, proteins in animal origin are superior than the proteins in plant origin. There are two important reasons for the superior nutritient quality of proteins in animal origin. One is the fiber existence in plant origin products. Fibers are complex carbohydartes, but they have tougher and more rigid structure when compared with the ordinary carbohydrates. Simple sugars in fibers are connected each other so strongly that stomach acid and the enzymes exist in intestines are not sufficient to decompose them. Therefore, they are excreted out of body without digestion as in the form of faeces and urine. But, the same compounds are antiaging and very protective against many diseases and disorders such as cancer and diabet. Although they are not absorbed and transferred through the mucosa of intestines, they bind the excess amount of carcinogens, salt, sugar, cholesterol, fat, high density lipoprotein (bad cholesterol), uric acid, histamin and many other biogen amines and eliminate them out of body by the means of faeces. Briefly, they are not absorbed, but they also prevent the fibers from absorption through the mucosa of intestine and help for the elimination of all these harmful compounds. This effect remains the salt, sugar and fat levels low in blood and the body automatically may be protected against diabetes and cancer. The consumer should never forget that, we need to

clean up our blood many times from all kinds of its dirts. Cholesterol and bad cholesterol, excess amount of salt, many food additives such as nitrit, nitrate, monosodium glutamate, trans fatty acids in margarin, sugar coming from candies, bread and pasta products, hormones of hormone added food products, fat and oil from fried and fast food products go beyond the walls of blood vessels and accumulate on the surface. The accumulation of all the mentioned harmful substances on the surface of these walls decrease the diameter size of the vessels and may cause thrombose and emboly that you can easily remember from above. The decrease in diameter size of blood vessels and insufficient level of blood supply into organs and their tissues, atherosclerosis, is the main cause of many metabolic diseases and disorders such as hypertension, liver and kidney failures, obesity, stroke, insomnia, Parkinson, Alzheimer, manic depression and even diabetes, since fats and sugars on the walls can be converted to simple sugars and can raise the serum sugar levels. Briefly, the calcified coating on the surface of calcified vessels become a kind of resorvoir which gives many harmful components to blood, organs and tissues. Excess amount of fat, oil and sugar is not only the cause of calcification, but they may cause various kinds of cancer. Because, the excess amount of fat, oil and sugar means the excess level of oxidation. Greater amounts of oils, fats and sugars enter into the reaction to be combusted by oxygen. The end product is free toxic peroxy radicals besides energy. But, they are in greater amounts than the normal occasions due to the calcified resorvoirs on blood vessels and sugar and fat rich consumptions. Excess of free toxic peroxy radical compounds may be converted into carcinogens. The production of carcinogens in lower amounts may be tolerated but there is always a possibility that they may even rupture the cell membranes and enter into cell in case of their great amounts. First, these harmful compounds, if they are in great quantities, may make a mechanical pressure against the wall and can rupture it and make entrance into the cell. Then they may decompose DNA, the genom of the cell and mutuate it. The cells begin to proliferate in greater amounts, followed by the mutation and decomposition of genom material because of the huge amounts of free toxic peroxy radical compounds. In conclusion, the consumers should be conscious and should not forget that, sugar,

fat, oil and salt do not only cause the calcification of blood vessels and important metabolic diseases, but also may cause cancer by increasing oxidative stress and its free toxic peroxy radical products.

We, as the consumers, should learn how to remain these harmful compounds in our blood serum lower by the means of food and nutrition. We have got an important weapon and a very effective weapon to be able to decrease their amounts in blood serum. This weapon is 'fiber'. As it is mentioned above, they are not absorbed, but they also prevent the absorption of harmful carcinogens through the mucosa cells of intestines.

We always tend to consume apple, tomatoe and peach by peeling. Many of us do not know that we are also eliminating a great amount of antioxidants; vitamines and isoflavones, antioxidant pigments and also fibers which exist in the skin of fruits and vegetables by peeling them. If the product can be consumed without peeling and if the skin is not too hard, then please do avoid from peeling and consume directly with skin parts. When it comes to vitamin A and its precursors namely beta karoten which are exist in greater amounts in these skin parts of fruits and vegetables, these vitamins will have been activated by cooking process and the consumer will be able to benefit from these antioxidants more. The rich amounts of vitamin A and beta karoten of fruit and vegetable skin may protect you from cancer and many other important diseases and disorders including hypertension and diabet.

Fibers are the cleaners of intestinal cavity which remove carcinogens out of intestines but their timing is important!

The germ of a cereal contains three parts; the outer layer which covers the inside endosperm and protects it from outer harmful threats. The middle part is called as endosperm which feeds the germ with its rich B complex, selenium, zinc minerals and protein content. Finally, the germ is located on one side in endosperm tissue. The germ and the outer layer which is richest in fiber content are eliminated during flour production because they give dark color to the bread and pasta products. Thus, the germ which is richest in selenium, zinc, as the important antioxidant minerals, B complex vitamins and protein content were used to be eleminated in addition to hull in the past. Only the endosperm was ground and the flour produced was used in flour, bread and pasta

productions. Briefly, the end product of bread, pasta and pasta products were deficient of the mentioned minerals and vitamins; B1, B2, B3, B5, B6, selenium, zinc in addition to protein during 80s and 90s. The researches about cereals and legumes, the rich vitamin, mineral and fiber contents of the hull and germ revealed the importans of the fiber and fiber rich components. Now, we are more conscious of the rich fiber, vitamin and mineral content of these parts in a kernel. Therefore, some people give sufficient importance to fiber rich foods, otherwords whole and unprocessed pasta and pasta products.

We, the consumers face with the two important details in considering the nutritious and cancer protection status of fiber rich foods and food products. First, fiber rich parts are also rich in zinc, selenium, some of B complex members that all these minerals and vitamins are also strong antioxidants which mean that they can make a significantly important protection against cancer and other metabolic diseases and disorders. Especially, the importance of fibers and fiber rich foods in cancer protection stems from their protection against diseases and disorders in stomach and intestine origin.

The regular consumption of fiber free foods and food products and poor nutrition from fiber for long years cause the accumulation of animal origin proteins on the surface mucosa of intestine and stomach. As it is mentioned above, fibers are only exist in plant origin products, they are in plant origin while all animal origin foods and food products are free of fiber. The high amount of proteins in animal origin without fiber accumulate on the surface of mucosa of intestine since there is no any fiber to push them through intestines and rectum. Hence, fibers are the main substances to form feces and they are the real means to eliminate all the dirt and sticky material from the surface of mucosa of intestine out of body. Fibers are not absorbed through the mucosa of intestine in proper amounts since they are very resist against acidity and enzymes because of their rigid and hard structures. Thus, they are not absorbed and they are not transferred into blood. They only stay in the cavities of stomach and intestines. While they are excreted out of body by the means of feces, they also prevent the absorption of the harmful compounds such as sticky animal origin protein compounds, excess of salt, many cancerogen substances, excess of cholesterol, bad cholesterol,

homocytein, trans fatty acids, excess of salt and hormon residues. Particularly, protein substances in animal origin can bind some other particules of salt, sugar, cancerogens, fat, trans fat and they continue to bigger in volume while their pressure against the beneath tissue becomes greater. These accumulated particules form sac. Such sacs always tend to accumulate the mentioned particules with carcinogens in their cavities. The small creatures, microorgansims, especially bacteria in the tissues which surround these sacks penetrate into these sacs since the nutrients, especially animal origin proteins in them, are the main nutrients for their survival. They invade these sacs, use the nutrients in them and decompose them. They use these sacs a kind of their proliferation sources. All required vitamins, minerals, high quality proteins, water and fat are exist in these sacs which are essential for their survival. They decompose some of the complex protein compunds in these sacs into simple amino acids and finally biogen amines to be able to digest them. Especially, biogen amines may sometimes be a precursor for carcinogen formation. In conclusion, the animal origin protein compounds in the sacs may be used as a carcinogen reservoir by the time if the consumer still insists on consuming 'fiber and water poor or free nutrition'. Especially the two substances; 'water and fiber', play an important part by rinsing the accumulated fat, protein residues, which are exist in these sacs. But, their effect can be possible in the early stages of the sac formations provided that these sacs should not be too deep and large in diameter size. The deeper the cavities of such sacs are, the more difficult the rinsing and cleaning process of these sacs by water and fiber are. Such sacs are called as 'diverticul' in medical platform. If the consumer can take preventive measure that is definetely a fiber and water rich nutrition and dominate such nutrition type in life style, then the risk of diverticules and the risk of cancer due to these diverticules may be avoided. Constipation may be an important indicator that the consumer may have a diverticul. It may also an indicator for the consumption of too much animal origin protein while neglecting fiber and water consumption. Changing nutrition style from animal origin to fiber and water rich nutrition while not neglecting high quality animal origin protein, may stop constipation and the progress of diverticul formation and thus, the formation of a cancer risk in digestive track.

There is another indirect anticarcinogen effect of fibers. They regulate the function of bile acids. Bile acids are responsible for the penetration of cholesterol, vitamin D, cortizol, oestrogen and testesteron into intestines. Their concentration in blood stream is an important determiner for some types of cancer. Some group of bacteria and fibers bind and consume some of these substances and regulate their concentrations in blood stream in balance so that any cancer formation and risk can be taken under control. Here below are some of the fiber richest foods and they may prevent the consumer from the high risk of cancer formation as long as they are exist in plenty amounts in kitchen and life style.

Whole bread, whole(unprocessed pasta products), lentil, barley, rye, bran, nut, cucumber, apple with skin, peach, potatoe, brokoly, Brussel sproud, white cabbage, spinach, celery, arthicoke, apricot, green pepper, sweet potatoe, whole wheat flour, flax seed, soy bean, pea, leek, dry bean, lettuce, radish, mint, thyme, eggplant and cabbage.

Soy proteins are one of the initial plant origin proteins while animal origin proteins except fish meat proteins and whey proteins, are high risk proteins from the point of cancer:

When a protein is concerned by the consumer as related to its quality, two factors should be known. One of them is the 'Net Protein Utilization' (NPU) and the other one is the 'biologic value'(BV). Net Protein Utilization (NPU) gives you the amount of absorbed protein which is absorbed through the mucosa of intestine followed by their digestion by stomach acidity and intestinal enzymes. The amount of these digested proteins from 100 grams of protein is called as NPU. Animal origin proteins which are blamed many times since their regular consumptions in huge amounts are responsible for the formation of many metabolic diseases including cancer, are the proteins which have got higher NPU values. Their NPU levels range from 70 tol00 % while many of the proteins in plant origin are lower than 70 %. What I mean here is that we are talking about the adverse harmful effects of proteins in animal origin on human body while we are not considering their high quality. In fact, we face with a reality that proteins in animal origin seem to be responsible for the formation of many metabolic diseases and disorders including cancer but this reality is exist only if they are fatty.

The low fatty meat and meat products, milk and dairy products, poultry products are always far from the risk of metabolic disease formation. What makes a red meat or a poultry meat is harmful is its fat content and it is always possible for the consumer to chose them as in low fat. But, the problem at this point is that, we are unable to seperate their fat content completely since some of these fat particules are so closely integrated into the meat proteins that the elimination of the closely incorparated fat part is impossible to be seperated. Placing the red meat or poultry meat bulk into the pan and covering the surface with water and boiling for only 1 minute and seperating the yellow fat globules on the surface of boiling water may be effective in reducing this fat content. Unfortunately, this application, prior to the main cooking process, can also eliminate a limited level of fat from meat, while some significant amount of fat still continues to be exist. The most important point here is that, the main nutrient group which is mainly responsible for the formation of many metabolic disesases including cancer is 'fats' rather than 'proteins'. This does not mean that proteins do not have the risk of cancer or any other metablic diseases and disorders. But, as long as they are consumed in moderate amounts as 'lower fat'or 'non fatty', the body can utilize them for body weight, muscle strenght, body lenght, blood cell proliferation, hormon production and many other beneficial metabolic functions in body. The main difference in the risk of cancer and other metabolic diseases between proteins and fats is the high rate of combustion of fats whereas proteins are not combusted by oxygen to give free toxic radicals as long as the body are not deprived of fats and sugars. First, sugars and then fats are combusted in cells by oxygen to give energy and free toxic radicals. Proteins are always used for the production of hormones, blood, bone, tissue and cell. Therefore, the main structral components of body are proteins while sugars and fats are used as fuels. But, they always yield free toxic peroxy radical compounds which are completely harmful for body. The excess amounts of them, especially the invisible fats in the meat and meat products, fatty milk and dairy products, can easily be combusted by oxygen in each cell of our body. After the combustion, they yield free toxic peroxy radical compounds. Excess of the free toxiic radicals can rupture the cell membranes of the cells, enter into the cells from these ruptures and

can decompose cell genome, DNA. Briefly, not definitely, but there is always a possibility that the long term regular consumptions of fatty dairy and meat products in huge amounts for long periods may cause cancer. For all these reasons, proteins are the least to be blamed for the formation risk of cancer and other metabolic diseases as long as they are consumed as in low fatty or non fatty. Only, they have got two risks from the point of cancer and other metabolic diseases that they are rich in 'iron' and 'biogen amines'. Too much protein consumption cause too much digested protein end products in the cavity of stomach and intestines. The enzymes of intestine and also the acid in stomach degrade the complex proteins until they are converted into biogenic amines. Biogenic amines can make entrance into the cells and change the genom of cell and may be responsible for cancer formation. No one can say that, it will be a definite result of protein and especially animal origin protein consumption, since there are also many other reasons ana factors for cancer formation apart from food and nutrition. But, 'food and nutrition' is one of the most important reasons for cancer formation and may be responsible for cancer if it dominates too much fat, oil, sugar, fatty proteins and protein consumption.

One parameter in addition to NPU is Biologic Value (BV) which informs you about the utilization level of protein in bone, muscle, blood, hormon and tissue productions. The greater the BV is, the greater its utilization capability for the future metabolic activities will be. Animal origin proteins always have got greater NPU levels as compared with proteins in plant origin. One reason for these higher NPU levels is due to fiber inexistence in animal origin proteins. Fiber, the complex carbohydrate substances in plants; vegetables, fruits, cereals and legumees, are antiaging. Because, they can bind various harmful substances such as bad cholesterol (low density lipoprotein), excess of the salt, fat and sugar, homocytein, trans fatty acids, omega 3 fatty acids, many carcinogens, food additives, allergens, as indicated above. They excrete them by binding and cause their elimination out of body by the means of feces. That is why fiber rich nutrition is always a cornerstone for a healthy lifestyle and nutrition and also very effective in prevention from many metabolic diseases including cancer and cardiovascular diseases such as stroke and hypertension. Fibers, our antiaging weapons

against diseases and aging, has got one important disadvantage that, they not only bind harmful substances, but can bind some important and beneficial substances like omega 3 fatty acids, important vitamins and minerals, essential amino acids, drug substances. As a result, fibers decrease the bioavalibility of all the mentioned beneficial substances by eliminating them out of body by the means of feces. Proteins are one of the most important nutrients in our foods. They are utilized for blood, bone, tissue and hormon productions in body. Body lenght, the strenght and resistivity of bones and muscles against defects and extrinsic pressures and therefore, the protection against osteoprosis and osteomalacia, the proliferation of skin cells, hair folicules, are all possible by the means of proteins. These nutrients are the structural components off all tissues in body. For this reason, our intestines should be able to absorb sufficient amounts of proteins and transfer them into blood without binding by fibers. On the other hand, fibers can bind them and decrease their bioavalibility. Fibers are plant origin and they are never exist in animal origin products. This is an advantage, but also a diasadvantage, because proteins in animal origin can be absorbed and transferred into blood in greater amounts when compared with the proteins in plant origin, since they are not bound by fibers. Briefly, the quality of protein, the NPU and BV levels in proteins in animal origin products, are always higher than plant origin products because they are free of fibers. But, the absence of fibers in animal origin foods and proteins may also appear a great disadvantage since the cavities of intestines of the consumers who neglect the consumption of sufficient fiber rich foods, are always deprived of fibers. Hence, the carcinogens in their intestines can find no chance to be push, bound and eliminated by the means of feces. Therefore, fiber free nutrition, the consumption of fiber free foods can make the consumer liable to cancer. A fiber free nutrition can always be an important factor in increasing cancer risk and it is always one of the possiblities among the reasons of cancer. I want to underline here is that proteins in animal origin have always more quality than the proteins in plant origin proteins. Because they are free of fibers and hence they have got higher NPU and BV levels. Unfortunately, when we consider the health benefits, antiaging status and preventive capability against diseases and disorders, proteins in plant origin appear

as more beneficial with their rich fiber contents, in spite of their lower protein quality. The consumer should evaluate the mattter in different platforms. If the target is a rich nutritious status of proteins with their body lenght, strenght and power increasing effects, we can benefit from animal origin proteins. If the consumer is energetic and runs an active life style while making regular sport and exercise all through the week, 5-6 times a week without missing, then, such consumer may be able to show more tolerance of the fat in animal origin proteins. Because they can convert the high cholesterol and bad cholesterol into testesteron, vitamin D, bile acids, dopamin, seratonin, melathonin, the important neurotransmitters that regulate the circulation of electricity through brain tissue, by the means of activity, regular sport and exercise. A body younger than 30 years age, can utilize the excess of fat, cholesterol and bad holesterol by converting them into the mentioned beneficial substances. In conclusion, the consumer should always concern about the harmful effects of fatty proteins in animal origin, since they are rich sources of cholesterol and bad cholesterol and saturated fat. But these risks should never be exaggerated, because some factors such as 'being younger', 'weight loss', 'an active lifestyle', 'regular sport and exercise', 'a life style free from alcohol and nicotine', can reduce the risks coming from cholesterol and fat rich animal origin proteins. We desperately need high quality proteins which are exist in animal origin foods if we are young and active, if we are familiar with regular sport and exercise and we have a clean history free from cancer in our parents and our previous generations. From another different corner, if the consumer is the one who runs a lifestyle with a heavy stress while neglecting sport and exercise but using alcohol and nicotin and consuming animal origin foods in huge amounts for long periods, there may always be a risk to face with the risk of cancer. This time, the consumer will not be able to tolerate the excess amount of cholesterol, bad cholesterol and fat which in animal origin. These substances accumulate inside blood vessels and hence, can cause calcification while excess of cholesterol, saturated fat and bad cholesterol can be converted into carcinogens. The risk due to animal origin rich nutrition, may depend on various factors. Blaming animal origin proteins as the only culprit for the risk of cancer and many other metabolic diseases and disorders is not

so easy. The consumer should consider many different factors while evaluating the risk coming from animal origin rich foods and proteins. But, the consumer should also concern about the higher quality with the essential and uncomparable beneficial effects of these proteins on our body. Many people do not know that many times media do neglect to inform the consumer about the preventive actions of animal origin foods. Only, the regular consumption of fatty animal origin foods and proteins in huge amounts for the long periods of life may be responsible for the formation and progress of cancer and many other metabolic diseases. The same proteins can protect against anemia with their rich iron quality, can protect against Parkinson and Alzheimers Disease, Chronique Fatigue Syndrom (CFS) with their rich B12 and B complex vitamin contents. The most important reality which should be taken into consideration while evaluating the risk status of animal origin proteins from the point of cancer risk should be some other various and important factors. The consumption rate, the amount, the activity level, the life style, age, sex, fat content of the animal origin protein rich food, sport and exercise and the family profile, are some of these important factors which determine the risk that comes from animal protein rich food sources. The consumer who has one or some of these problems should consider about the consumption of animal protein rich foods and avoid from the consumption of them as long as they are fatty and in huge amounts.

The higher quality of animal origin proteins is not only due to being free of fibers and higher bioavalibility, but also they contain higher quality calcium and iron while they are rich in vitamin B12 and other members of B complex. Vitamins of B complex and B12 are essential for the production of neurotransmitters which are responsible for the circulation of electricity and stimulation of important centers in brain tissue by electricity. Therefore, the stimulation and the function of brain tissue can only be possible by electricity which can be supplied by these nerotranmitters, namely; dopamin, seratonin and melatonin. The production of all these neurotransmitters is deathly important for the brain stimulation and function. It seems very clear that, when the importance of vitamins B and B12 on brain function is concerned, the roles of these vitamins become more and more important. One of the

most common diseases of today's world is Alzheimer besides Parkinson and both diseases may form due to the deficiencies of B12 and other members of B complex. Statistics reveal that many cases of Alzheimer and Parkinson indicate to the deprivation of B12 and vitamins of B complex. Thanks to proteins in animal origin including milk and dairy products that, they are richer in B12 and vitamins of B complex whereas especially B12 is not exist in many of the plant origin foods and food products. The same vitamins, B12 and other vitamins of B complex are also essential for the proliferation of blood cells. Hence, the protection against anemia always requires the domination of B12 and vitamins B rich foods and food products such as animal origin proteins.

In conclusion, an attitude to blame animal origin foods and food products for many metabolic diseases and disorders including cancer is not a corrrect and a conscious approach. A healthy nutrition and life style can not be without high quality animal origin proteins, since they are the essential structural componennts of our cells, tissues, hormones, blood, bones and muscles. They are also very effective in preventing from anemia, Alzheimer and Parkinson. One of the most common factors contributing to disease progress is the fat content of animal origin proteins. The consumer should evaluate the status of the fat in two ways. One way of the consideration should be the visible fat which covers the inner meat tissue and the surface of meat bulk which can be seen by naked eye. This fat may be evaluated as innocent since the consumer can easily eliminate it by using knife manually. Also, this visible fat can easily show itself and informs the consumer about the fat content of the meat product at first look. The second way of the evaluation is a little bit more difficult since this kind of fat tissue is so closely integrated into the meat protein particules that, it is impossible to seperate these fat globules and protein globules from each other manually. On the other hand, the same fat type can also not be seen by the naked eye as opposite to the visible fat, the cover fat, the tail fat or the inner fat which accumulates in the cavitities of intestines, on the surface of kidneys. In conclusion, every meat type incuding red meat or poultry meat always contain less or high amount of fat which may be visible or invisible while the visible part can be eliminated as manually while the inner fat can easily disguise itself. That is why

even the less fatty meat and meat products should always concerned as having got higher risk in cancer nutrition. There will also be some other different factors which will affect their risk status such as sex, age, sport and exercise, family history, life style, alcohol, nicotine, the regular consumption rate and the amount. In a cancer nutrition program, elimination of red meat and meat products completely can not be a conscious solution and correct approach, since these products are the richest sources of B12, the vitamins of B complex, high quality iron and calcium and important essential amio acids which are utilized for the production of bone, muscle, blood, hormon, tissues and cells. What is the solution during cancer or against cancer?; Avoidance from animal origin food consumption in huge amounts while prefering the less fatty meat and meat products, milk and dairy products.

One of the most effective ways for the protection from cancer by the means of foods is the heavy consumption of antioxidants, especially vitamins A, B and C. The consumer can be protected against cancer and can lower the risk of cancer by the means of these antioxidants. The consumer may also help for the control of cancer progress as complementary to medical treatment with these vitamins. A person with cancer or without cancer should dominate the foods rich in antioxidants, not only for the protection against the disease, but also these antioxidants and other antioxidants can deplete the production of the free toxic peroxy radicals which may be converted into carcinogenes. Many cells of the tissues and organs are under the thread of these harmful free radical compounds, every day and every seconds. Many of the cells in eyes, liver, cardiac tissue, intestines, stomach, skin and in every other organ and tissue are wounded by the effect of these harmful compounds day by day. The increase in the ratio of these wounded cells due to free toxic peroxy radicals is the main cause of organ failures and organ aging. Of course, new young cells will continue to replace the older or wounded ones, but here, the degree of harmful free toxic compound production is the main determiner. No matter how the antioxidant entrance in plenty amounts is exist, as long as the consumer insists on consuming fat, oil, sugar and salt rich foods more than the foods rich in antioxidant capacity, organs and tissues will continue to be under the thread of toxic radicals. As a result, the consumer will continue to face with a possible

risk of cancer formation because of the high rate of free toxic peroxy radical production in body.

The two important means to be protected against cancer or take it under control as complementary to medical treatment are; 'fiber' and 'antioxidant'. Here below are some of the initial foods which ae rich in vitamins; C, beta karoten as the precursor of vitamin A and E. Do eat these foods as in the list of cancer diet in every period of your life if you are not suffered with cancer. Because the anticancer diet in a patient with cancer should change depending on the type of anticancer drug!!!.

Among vitamins, the most functional one is vitamin C. It does not only decrease the risk of cancer, but also diabet by decreasing blood sugar concentration. The vitamin also increases dopamin, seratonin and melathonin, the neurotransmitters which regulate the electric transfer through the brain tissue. Therefore, the vitamin is essential in protection from depression, insomnia, Parkinson and Alzheimer's Disease. Vitamin C shows its anticarcinogenic effect most in liver cancer. The vitamin is claimed to decrease the risk of lung cancer caused by nicotin.

	Vitamin C	Beta karoten(mg)	Vitamin E
Apple (medium)	8	0.04	0.44
Brokly	116	1.30	1.32
Whole rice	0	0.00	4.00
Brussel sproud(250g)	96	0.67	1.33
Carrot(medium)	7	12.00	0.28
Cauliflower(250g)	54	0.01	0.05
Chicken meat(250g)	2	0.02	0.57
Corn(250g)	10	0.22	0.15
Grapefruit(half)	47	0.19	0.31
Dry bean(250g)	2	0.00	4.10
Orange(medium)	75	0.16	0.31
Pineapple(250g)	24	0.02	0.16
Orange juice(250g)	124	0.30	0.22
Soy bean(250g)	3	0.01	3.35

Spinach(250)	16	2.30	0.57
Strawberry(250g)	84	0.02	0.23
Sweat potatoe	28	15.00	0.32

FIGURE 1

According to the figures above, one of the richest vitamin C source is grapefruit. In spite of its rich vitamin C content, the fruit should be avoided during cancer treatments since bergamottin in the fruit inhibits cytochrom P 450, a group of enzymes in liver which is repsonsible for detox. These enzymes are so important that any toxic substance including carcinogenes, like free toxic peroxyradicals, excess of cholesterol and bad cholesterol, homocytein, harmful food additives; like excess of nitrate and nitrite can be detoxified by the enzyme system. Additionally, radio and chemotherapautic agents which are applied during cancer treatments are also detoxified and eliminated out of body followed by their anticarcinogen effect by the same enzyme system. Bergamottin in grapefruit may inhibit the enzyme system and cause accumulation of the concerned radio or chemotherapeutic agents in blood or tissues. The result May be very harmful and toxic for body since the excess of these agents begin to attack not only cancer cells but also healthy cells, tissues and organs. Briefly, if the consumer still continues to consume grapefruit because of its rich vitamin C content during cancer treatments, this may adversely be effective and even may be fatal by increasing the side effects of anticarcinogen treatments because of its mentioned effect mechanism. Therefore, no matter how rich its antioxidant capacity is, including its vitamin C content, the consumer should avoid grapefruit consumption when suffered with cancer or during anticancer treatments.

The information as related to the anticancer effect of vitamin C, E and beta karoten is well documented and also commonly known by a great number of people. But, many countries or regions still do not know the protection capability of cruciferous vegetables especially brokoly, Brussel sproud and white cabbage. First, the mentioned foods have got a rich content of vitamin C and B that are water soluble vitamins while having got a great anticarcinogen function. Additionally, the main

substance which act as anticarcinogen in these foods is 'isothyocyanate'. Each of the mentioned vegetables contain the substance, but the consumer can increase isothyocyane content by mixing and consuming them together as in salad form. The cutting process during salad preparation may decrease vitamin C and B contents. But, the effect is opposite for isothyocyante. This group of bioflavonoids may even be activated by cutting process. A little amount of vinterized olive oil to this salad increases the benefit from vitamin A since the vitamin is a fat souble one and can be absorbed through intestine and transferred into blood when solubilized in fat. The consumer can also add some rindered garlic since this vegetable is one of the richest plants which has a rich isoflavon content.

Another address for creating an anticancer diet is soy and soy products. These foods contain 'daidzein' and 'genistein' bioflavonoids. These substances compete with the harmful oestrogen form which increases the risk of mammary cancer and bind the estrogen receptors before the harmful oestrogen forms. So, the cancer effect of these harmful oestrogens can be minimized by the means of daidzein and genistein in soy and soy products. On the other hand, it is still a matter of debate that daidzein and genistein in soy and soy products are very similar to female hormones, oesterogens, with their affinity to the same receptors and their structures. Thus, the excess intake of them into body may increase the risk of mammary and chest cancer which is normally caused by the harmful form of oestrogen. Briefly, daidzein and genistein in soy and soy products may alter hormonal balance, especially in favor of the harmful form of oestrogen and may increase the risk of mammary and chest cancers when they are consumed in excess amounts. If the consumer has elterns with a chest or mammary cancer history, or bad habits like nicotin or alcohol, or is not friendly with regular sport and exercise, but instead, consumes too much red meat and dairy products, then the consumption of soy and soy products may not have protection against cancer, opposite, may increase the risk of cancer. It is still a debate whether soy and soy products can make a definite protection against cancer, since there are many scientists and studies that show the similarity between estrogens and soy daidzein and genistein. If the consumer is free of cancer, does not have a cancer history in the

previous generations and family, if free of alcohol and nicotin and makes regular sport and exercise, then medium amounts of soy and soy products, two or three times a week, may increase life quality. Because daidzein and genistein can also lower cholesterol and bad cholesterol while dilating blood vessels and support blood circulation. The same benefits can also be possible by the means of vitamin B, C and beta karoten as the precursor of vitamin A and also isoflavonoids namely exist in brokoly, Brussel sproud and white cabbage. In conclusion, the consumer may not only decrease the risk of cancer, but also the risk of cardiovascular diseases and disorders like hypertension and stroke by the means of the mentioned foods.

Every day, thousands of cancer cells form in human ana animal body. But immun system and the cells of the system inhibit the proliferation of these cells and lower the risk of cancer. Therefore, cancer, as one of the most important metabolic diseases, is a result of immun deficiency. If cancer is described as an immun deficiency disease, this definition is not wrong. Stress, poor antioxidant intake, fiber free nutrition, insufficiency of high quality protein, a life style which is lack in regular sport and exercise, are all the predisposed factors increasing the risk of cancer. Each of them cause a deficiency in immun system by forming too much toxic radical which kill immun system cells that inhibit cancer cell proliferation. Here below are the initial factors in life that increase the risk of cancer;

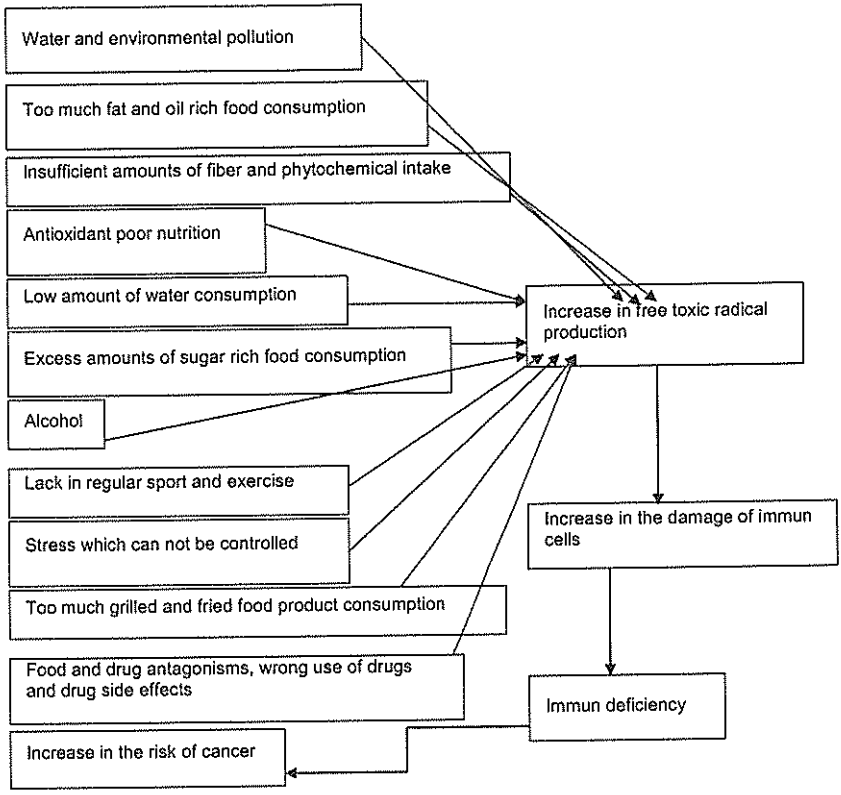

Water and environmental pollution
Too much fat and oil rich food consumption
Insufficient amounts of fiber and phytochemical intake
Antioxidant poor nutrition
Low amount of water consumption
Excess amounts of sugar rich food consumption
Alcohol
Lack in regular sport and exercise
Stress which can not be controlled
Too much grilled and fried food product consumption
Food and drug antagonisms, wrong use of drugs and drug side effects
Increase in the risk of cancer
Increase in free toxic radical production
Increase in the damage of immun cells
Immun deficiency

FIGURE 2

When it comes to vitamins

Vitamin A deficiency contributes to cancer by using a hidden mechanism in body which defects immun system. Most of us know the vitamin with its boosting effect on immun system and visual health. The vitamin is an important weapon for us in antiaging which enable a healthy aging, while making the body resist against diseases by inhibiting free toxic peroxy radical compunds. This effect is the same with the antioxidant effect of all other vitamins and minerals. But, another important function of the vitamin is also important since the deprivation of body from this function can easily make body susceptible to diseases and disorders and a weak immun system. Microorganisms make their entrance into body by using cavities such as eye, ear, anus, nose. These organs are covered with a mucus coating which is made by vitamin A. Microorganisms can be kept by this coating and their enterence into the deeper tissues may be prevented. In case of the vitamin deficiency, this coating can not be produced in enough amounts and microorganisms may invade the body easier. Moreover, the worst risk is the enterance of microorganisms into the deeper tissues. Under normal conditions, the surface of the organs are also covered by a coating which is produced by the vitamin. But, in case of the vitamin deficiency, another coating substance which is much drier and solid is produced. This substance may defect the smooth tissue under and can even cause small bleedings. Blood is a perfect media for microorganisms since it is very rich in protein, sugar, fat, vitamin, mineral and water. Briefly, blood attract the microorganisms including the pathogen ones, since it is a perfect media for their proliferation and activity. At one time, there may be several infections in many parts of the body, may be a sequence of infections or continued infections. Many people under the vitamin deficiency often complain about chronic fatique, ana/or a mild fever. The common complaint is that they always become suffered with another disease or disorder after they are treated for the previous disease. The deficiency of the vitamin may be neglected in many occasions while other blood parameters are taken into consideration. In many cases, including vitamin A rich diet

into life style, may solve the problem. Which foods are rich in vitamin A? It may be much easier to remember for the consumer that all green, yellow and red fruits and vegetables are rich sources of vitamin A and the consumer can easily remember this important information during Marketing. A table rich in yellow, red and green fruits and vegetables and similarly a refrigerator filled with the same vegetables and fruits will give the consumer the benefit of the vitamin. It May be useful to remind once more that the deficiency of the vitamin can easily weak immun system, may make body susceptible to diseases and disorders. Especially, the liablility of body to pathogen microorganisms such as *Streptoccocus faecalis*, *Campylobacter*, *Listeria* and *Clostridium* may trigger body's liability to cancer by weakening immun system. Cancer may be dominant in body only when the immun system is weaker because of poor nutrition, poor antioxidants ana heavy stres, in addition to vitamin A deficiency. Another important knowledge which can be helpful for the consumer in increasing the benefit of vitamin A in the diet may be the 'red color'. The more the red color in the concerned fruit or vegetable is, the more the vitamin A and its precursor beta karoten contents are. Therefore, the consumer should prefer the intense red colored fruits and vegetables. For example, the redder tomatoes always an indicater for the richer vitamin A contents. Like color, another parameter, which increases the vitamin and its antioxidant effect, is the 'heating process and vitamin concentration'. Heated and concentrated fruits and vegetables are richer in the vitamin. For example, a ketchup product is richer in antioxidant capacity of vitamin A when compared with tomatoe. Another important factor which affects the bioavalibility of the vitamin is that the consumer should always add one or two drops of vegetable oil into tomatoe juice, ketchup or even into salads, prepared by fruits and vegetables rich in the vitamin. Because the vitamin is fat soluble and it can only be absorbed with some oil through the mucosa cells of intestines and transferred into blood. On the other hand, these details given here, are only for this vitamin, but not for the other vitamins, namely vitamin C. Vitamin C shows the opposite atributes. It is not fat soluble, but it is water soluble and it can even lose its antioxidant capacity when its food source is heated or concentrated, as opposite to vitamin A. Since it is water soluble, but not fat soluble, addition of fat

will be meaningless. If the target is to benefit from vitamin C rather than vitamin A, heating, cutting, freezing, grilling, scalding, concentrating, all may cause the loss of the vitamin in significant amounts. Some fruits and vegetables are both rich in vitamin C and vitamin A. Under these circumstances, the fruit or vegetable batch may be divided into two equal batches and the consumer can increase the antioxidant effect of one batch by cooking it while consuming the other half without cooking. Both of the vitamins are strong anticarcinogens due to their various mechanisms. The foods rich in both vitamins may reduce the risk of various cancers in a healthy person.

Nuts should be in moderate amounts, but plenty amounts may be a risk in increasing the formation of cancer and other metabolic diseases!

The important benefits of nuts are their rich antioxidant contents such as selenium, zinc, calcium, iron and the members of vitamin B complex. All the mentioned antioxidants inhibit free toxic peroxy radical formation. When the convertion of free toxic peroxy radicals into carcinogens and sugar, it may give some benefits in the prevention from diabet to cancer. On the other hand, nuts are richer in lipid (fatandoil) content and especially omega 6 fatty acids except walnut. Below are the saturated fatty acid amounts of pig meat, beef and chicken, followed by a detailed fat contents of nuts.

	Saturated fatty acids/g
Pork, fresh, spareribs, separable lean and fat, cooked, roasted	11.12
Pork sausage, fresh, cooked	8.79
Pork, fresh, loin, country style ribs, separable lean and fat, cooked, braised	8.01
Beef, ground, 75% lean meat, 25% fat, cooked, broiled	7.25
Beef, rib, whole (ribs 6-12), separable lean and fat, trimmed to ¼ fat, alll grades, cooked, roasted	11.70
Chicken, broilers or fryers, wing, meat and skin, cooked, fried, batter	5.83

Average nutrient composition of nuts (per g). US Department of Agriculture Nutrient Data Base at: http://www.nal.usda.gov/fnic/cgi-bin/nut_search.pl (Accessed on 26 April 2010).

Nuts	Energy (kJ)	PUFA (g)	LA (g)	Protein (g)	Fiber (g)	Folate (µg)
Almonds	2418	12.2	12.2	21.3	8.8	29
Brazil nuts (dried)	2743	20.6	20.5	14.3	8.5	22
Cashews	2314	7.8	7.7	18.2	5.9	25
Hazelnuts	2629	7.9	7.8	15.0	10.4	113
Macadamia	3004	1.5	1.3	7.9	6.0	11

Linolenic acid existence in a food including nuts is an advantage and a benefit from the side of consumer, since this essential fatty acid is the precursor of omega 3 polyunsaturated fatty acids. Lipids are divided into two classes as 'fats' and 'oils'. Oils are liquid because of their lower melting points under room temperatures and they are in plant origin. They are free of cholesterol because of their plant origin. Conversely, fats are solid because of their higher melting points under room temperatures and they are in animal origin. They are always integrated with high or low amounts of cholesterol. Both fats and oils are produced by combination of free fatty acids, which are the smallest structural components of lipids, with 3 value alcohol glycerol. If the fatty acid is 'saturated' which means that there are enough hydrogen atoms among their carbon atoms and complete in hydrogen bonds, such fatty acids produce fats, animal origin lipids, followed by their integration with 3 value alcohol glycerol. But, there are unsaturated fatty acids in nature besides saturated ones which are missing in hydrogen bonds among their carbon atoms because of their insufficient numbers of hydrogen atoms. Such free fatty acids are called as 'unsaturated' and when they are combined with 3 value alcohol glycerol, they produce plant origin lipids. Otherwords, oils which are free of cholesterol. As the figures above clearly indicate, it is expected that, all nuts will be free of cholesterol because of their plant origin. But, this attribute does not mean that they do not have any potential to raise cholesterol in body. Especially, two saturated fatty acids; palmitic and stearic acids, which are in higher concentrations in animal origin fats, since they are saturated, may reach liver in body after their consumption and digestion

and may be converted into cholesterol, bad cholesterol and oxidized bad cholesterol by liver. Briefly, not only the content of cholesterol and bad cholesterol in the concerned food, but also the ratio of saturated fatty acids, especially palmitic acid and stearic acids are the other important determiners in elevating total cholesterol and bad cholesterol levels of blood serum. The significantly important increase in cholesterol and bad cholesterol is not only a risk factor which triggers the formation of cardiovascular diseases and disorders such as hypertension, but also it is important for the risk of cancer since the excess of both compounds; cholesterol and bad cholesterol can be converted into carcinogens in body. In conclusion, the consumer should protect body from cholesterol, bad cholesterol and excess amounts of saturated fatty acids since they have an important potential in increasing the risk of cancer. Protecting body against excess amounts of cholesterol, bad cholesterol and saturated fatty acids will also have protected the consumer against cancer. Nuts may be defined as completely beneficial foods, but this kind of evaluation may not be scientifically correct, especially in the prevention from cancer and cardiovascular diseases and disorders. Because they have higher saturated fatty acid contents as clearly seen in the list above, no matter how they are free of cholesterol!.

The main protein source in an anticancer diet should be 'fish meat' while red meat and its products should be restricted and excess amounts, especially the fatty ones should be avoided. Red meat and its products, also milk and dairy products are not only rich in cholesterol and bad cholesterol, they are also rich in homocytein, trans and omega 6 fatty acids. Opposite to omega 3 polyunsaturated fatty acids, omega 6 fatty acids always have a potential to trigger to increase the risk of cancer by increasing a special protein which is called as 'Tumor Necrosis factor (TNF)'. On the other hand, 'omega 3 polyunsaturated' which are exist in plenty amounts in fish meat, flax seed and some vegetables and many of the seeds decrease TNF and therefore decrease the risk of cancer. Stearik acid and palmitic acids, the saturated fatty acids, are exist in red meat, milk and their products while they are saturated. In other words, omega 3 fatty acids are not only protective against cancer risk by decreasing TNF, but also they are free of stearik acid, palmitic acid and other saturated fatty acids which may be converted into cholesterol by

liver. Cholesterol and bad cholesterol may be converted into cholesterol in case of their abnormall high amounts as indicated above and body may be liable both the risk of cardiovascular diseases and cancer. One of the commonly consumed meat type is pig in Western countries and United States. The higher demand for the consumption of pig meat is mainly due to the meat yield and taste. The highest yield and volume of meat in pig as compared with many other livestock animals including cattle and lamb, make it the most commonly consumed one among meats in western life. But, the meat is also the richest in fat, omega 6, trans fat and saturated fat. Although it is cheapest, it is one of the most harmful one due to its rich omega 6, trans fat, saturated fat, cholesterol and bad cholesterol, all of which may be converted into carcinogens in the body and may increase the risk of both cardiovascular diseases and cancer. The separation of pig meat from cover fat as manually by using knife does not necessarily mean that the meat will be free of fat, since their marbling degree which may be defined as the integration and localization of fat globules among meat particles is higher in pig meat. Therefore, although the consumer may separate the surface fat, it is always impossible to separate the mentioned inner fat which is defined as 'marbling'. Heat application such as scalding and oven may melt some fat on the surface and at the buttom but the amount of this melted fat is not too much while the cooked pig meat still may yield excess amount of cholesterol, omega 6, bad cholesterol and trans fat. There is still exist no any definite and effective method to separate the fat globules and meat globules from each other because they are so closely integrated with each other. For all these reasons, especially pig meat and its products should be avoided and not included into the list in an anticancer diet. Although the same disadvatages are exist for red meat, milk and their products, their saturated and unsaturated fat contents are lower than the other meats. The best approach at this point is to avoid both pig meat, red meat, red meat products, milk and dairy products, while dominating fish meat and proteins in vegetable origin such as soy and its products May be a useful approach. Finally, when the consumer look for the saturated fat levels in pork, chicken and beef meat, it appears around 5-12 mg/g, whereas all nuts except almonds and hazelnuts have got the similar amounts of saturated fats!. All over

the world, people concern about saturated fats and their potential to cause cardiovascular diseases, vessel calcification (atherosclerosis). Constantly, informations to avoid saturated fats by the means of meat and meat products have been given by media and authorities, while nuts are informed as completely beneficial because of their antioxidant contents without considering their high amounts o saturated fatty acid contents!!.

Opposite to the red meat and its products, milk and dairy products, poulty meat, egg and their products, fish meat is rich in polyunsaturated fatty acids. Polyunsaturated fatty acids have got unsaturated bonds among carbon atoms because of insufficient amounts of hydrogen atoms. The unsaturated fatty acid number is more than one. If the number of such fatty acids is only one, these types of unsaturated fatty acids are called as 'monounsaturated'. Nutrition science always advises the equal ratios of polyunsaturated and monounsaturated fatty acids or a little bit higher ratios of monounsaturated than polyunsaturated ones. The reason is that, mono or polyunsaturated fatty acids, briefly unsaturated fatty acids, are much healthier than saturated fatty acids. There is always a potential of saturated fatty acids to be converted to cholesterol by liver as indicated above. It does not mean that unsaturated fatty acids have got no potential or risk. Because, they can also be converted into saturated fatty acids in body and then these saturated fatty acids may be converted into cholesterol. But, the mentioned mechanism is an indirect one whereas saturated fatty acids can be converted into cholesterol and bad cholesterol directly. The unsaturated fatty acids should be taken into body first. Then, they can be converted into saturated fatty acid and the formed saturated fatty acid in the final step can be converted to cholesterol and bad cholesterol. These convertions may form in case of unsaturated fatty acid consumptions in very huge amounts after long periods. Therefore, unsaturated fatty acids may be defined or advised as less harmful and risky when compared with saturated ones. On the other hand, saturated fats can easily and directly go beyond vessel walls and stick on them and finally may be responsible for the progress of calcification of vessels (atherosclerosis). This risk is less in polyunsaturated ones since they can be bound on the walls of vessels only after they are converted into saturated forms.

Another risk in cancer risk, Biogenic amines

Complex proteins are crucial since cells, their proliferation and their healing process after cellular damages can only be possible by proteins. But, for the utilization of proteins in all the mentioned activities, first, they should be decomposed into simple substances to be used by the cells in body. The smallest structural components of proteins are called as 'amino acids'. Other words, amino acids come together, connect each other and finally form complex protein compounds. The complex protein compounds are not suitable to be used and utilized by cells because of their complexity. Like all other nutrients, carbohydrates and lipids, they first come into the cavity of stomach. The stomach acidity degrades them into smaller particles such as peptons and peptides. Because they are still not enough smaller to be absorbed through the mucosa of intestines, these smaller digested protein particules pass into the cavity of intestines and they are decomposed and converted into the smallest components of proteins, amino acids, by the effect of special protein compounds, enzymes. Briefly, the complex proteins are degraded into the smallest compounds, amino acids, by the effect of both stomach acidity and enzymes. Amino acids can be absorbed through the mucosa cells of intestines and transferred into blood circulation and then they can reach into the cells in every parts of the body. Some amino acids may be degraded further by the effects of the enzyems prior to their absorption through intestines in the cavity of intestines. The decomposed parts left followed by the further decomposition by the effects of enzymes are called as 'biogenic amines'. Biogenic amines, in case of their high concentrations, may cause several metabolic diseases from calcification, hypertension to allergy. But, some of the abnormally high concentrations of biogenic amines may be converted into carcinogenes and increase the risk of cancer. Histamin, cadaverin, putressin, ornithin, histidin are some of the namely biogen amines. The most important factor which should be taken into consideration at this point is the difference in the production capabilities of animal

origin proteins and plant origin proteins. The biogenic amine production potential of animal origin proteins is higher than plant origin proteins. The initial reason is the fiber factor. Since the proteins in animal origin are free of fiber and fiber is only exist in plant origin proteins, there is always a possibility for the plant origin proteins to be bound by fibers which are integrated with the same proteins. But, because there is no fiber in animal origin proteins, these proteins and the formed biogenic amines from them can not be bound by fibers and they have an opportunity to be absorbed through the mucosa of intestines and transferred into blood without binding by fibers. Briefly, fibers not only bind carcinogens, exces of cholesterol, bad cholesterol, fat and oil, salt, some harmful substances such as nitrite and nitrate, but also they bind biogenic amines which might then be converted into carcinogens. Thus, the consumption of animal origin proteins in high amounts may yield high amounts of biogenic amines which can increase the risk of cancer. On the other hand, proteins in plant origin can also produce biogenic amines, but the ratio of the absorbed biogenic amines produced by these proteins are less since some of them can be bound by the fibers which are integrated closely with the same proteins.

Dietary Iron and Cancer

Iron is one of the most important elements for health in life since it enters into the structure of 'heme', a special protein in blood. This protein combines with another protein, 'globin' and produces 'hemoglobin', the special protein compounds of blood stream which carries oxygen into cells. Hemoglobin can not be produced without iron and hemoglobin can not form without iron. As a result, enough oxygen can not be transferred into cells because of insufficient concentrations of hemoglobin due to iron deficiency. So, what happens if enough oxygen can not be transferred into the cells of organs due to hemoglobin deficiency which is caused by iron deficiency? As previously mentioned, oxygen is inhaled and comes into lungs. Followed by, the gas is absorbed from lungs and pass into blood stream and comes into cells. The complex nutrients are consumed by the means of foods and they are digested by the effect of enzymes in intestines and stomach acidity. After they are converted into smaller and simple compounds followed by their digestion, they are absorbed through the mucosa cells of intestines and pass into blood. The nutrients are transferred into the cells in the organs by the means of blood cells while oxygen is transferred by hemoglobin. Only after these transfers, oxygen can be taken by the cell and combust the nutrients in the cell to yield energy (kalorie) which is utilized in all kinds of our metabolic activities. Briefly, the production of energy needs two musts; nutrient (especially carbohydrate, fats and oils rather than proteins) and oxygen. The carrier of this oxygen is hemoglobin which is made of iron. For all these reasons, iron deficiency causes hemoglobin deficiency which results in the deficiency of energy. Many people who are suffered with chronic fatigue have got iron deficiency and low concentrations of hemoglobin due to iron deficiency. Therefore, the rejection of all meats and offals because of their higher potential in increasing cancer risk can not be completely a correct and conscious approach. The high potential risk of red meat in increasing cancer risk was previously mentioned and and soon I will add the adverse effect of the rich iron content of such products in increasing cancer risk will be given later, but a complete

elimination of iron from the anticancer diet and lifestyle may probably protect the consumer against cancer and decrease its risk but while doing it, it may also increase the risk of anemia and chronic fatique sendrom. Milk and dairy products do not mean anything if the target is to supply enough iron content since they are deficient in iron and they contain trace amounts of iron. Additionally, they are at the top of the list of foods with higher risk of cancer because of their high biogen amine, trans fat, cholesterol, bad cholesterol, homocytein and animal origin proteins which are free of fiber. Briefly, the substances all of which can be converted into carcinogens. The trace of iron minerals in milk and dairy products in addition to their cancer risk increasing potentials make them out of the list in the diet and kitchen against cancer. But, elimination of milk and dairy products completely, is not a scientific, conscious and correct approach. Because, they have high quality calcium, vitamin B12 and other members of B complex, probiotics, magnesium, vitamins A, D, E and K and high quality proteins. The body can only be protected against osteoporosis (the liability of bones to fractures and the loss of the solid and tough structure of bones) and osteomalacia (the loss of muscle volume and strenght) by the means of milk and dairy products, while it can be protected against anemia and chronic fatique in a similar way, by using iron of meat and meat products, including fish, veal and poultry. In conclusion, the consumer has got no opportunity and luxury to eliminate all meat, milk and their products, because consumer may be deprived of calcium and iron followed by such diets and may easily be suffered with the mentioned diseases, no matter how they may decrease the risk of cancer. On the other hand, including fish meat from meats, and yogurt from dairy products, may still make the consumer resist against cancer, while protecting the consumer against anemia, chronic fatique, osteoporosis and osteomalacia. As it will be introduced in the part of probiotics, the friendly microorganisms which are not pathogen for human body and commonly used in food productions, may utilize some of the carcinogens or the harmful compounds such as cholesterol, bad cholesterol, saturated fat, very low density lipoprotein, homocytein, salt, sugar, nitrat, nitrit which may act as carcinogens. As a result, these microorganisms decrease their concentrations in the cavity of intestines and the risk of cancer formation especially in stomach and intestine

origin. Fish meat with its iron content may be a risk factor in cancer diet and kitchen. But its risk is always lower than other meats because of its richer omega 3 fatty acids which are strong anticarcinogens, in addition to its other anticarcinogens such as selenium, zinc, calcium, vitamin B12, vitamins A, D, E and K, magnesium, vitamin B6. After underlying the importance of yogurt and fatty fish involvement into cancer diet, it may be useful to continue the strong relation between iron and cancer.

Red meat and its products contain large amounts of iron. The form of iron (ferrous form) in red meat and its products can be absorbed through the mucosa cells of intestine easier than inorganic iron. Iron is also stored in a protein in tissues. The name of this special proteins which accumulates iron in tissues is called as 'transferrin'.

One of the reasons of the increase in cancer risk because or iron may be due to its free toxic radical increasing potential. If the iron which is consumed and transferred into colon cavity is still not absorbed and continues to be exist as in free form in the cavity, it can be combusted by oxygen in the cavity, can be converted into free toxic radicals and these toxic radicals may damage the mucosa of colon. This damage on colon mucosa can also trigger the formation of cancer on the surface of colon. Manganese superoxide dismutase is a strong defense factor of human body against free toxic radical compounds, but the iron supplementaion can cause the decrease of the enzyme which also explains the harmful effect of iron.

The main reason for the liability of persons with colit and ulcerative colit to colorectal cancer is their iron supplementation. Because of the improper function of intestines and colon, such patients are deprived of iron since dietary iron can not be absorbed through the mucosa cells of the inflammatory colons and they face with iron deficiency. Accordingly, they are prescribed with iron suplements and many times with megadoses to transfer iron across enterocytes and donate iron into circulation.

Caco-2 cells are human colorectal adenocarcinoma cells and increasing iron concentration in these cells is reported as the increase in oxidative damage in the same cells. Briefly, if the consumer is the one with cancer or colorectal cancer or colit or chronic ulserative colit,

should better decrease the consumption rate of iron rich foods, especially red meat and its products and offals.

Another cancer risk which is most adversely affected by iron is liver, as more than colon and rectum. The factors which increase the risk of liver cancer are mainly; viral hepatitis (the inflammation of liver by viruses), fat, sugar, alcohol, tobacco and finally iron. So, iron and iron rich foods are one of the factors in increasing the risk of liver which is one of the most important organs in our body that defends it against many microorganisms including viruses, bacteria species, molds and yeasts. The excessive accumulation of iron in hepatocytes (liver cells) cause defects and injuries in these cells. These defects and injuries may trigger the formation of hepatoma (the cancer of the liver cells) and fibrosis (the connective tissue production, fibrin, as a response and as a protection made by liver against a microorganism, an inflammation or to destroy cancer cells). Especially the fibrin tissue tends to accumulate among cells and make a mechanical pressure against liver cell walls. These injuries and defects on liver cell walls may also trigger the formation of liver cell carcinomas. If the patient is not treated and if fibrosis is not cured, the ratio of fibrin connective tissue in liver increases and causes liver failure which is called as cirrhosis. Cirrhotic patients are much more susceptible to the risk of developing hepatomas.

Another important detail as related to the carcinogenic effect of excessive dietary iron appears important for women rather than men. It should be concerned especially by women because of renal cancer increasing effect of both estrogen (female sex hormon) and dietary iron supplementation.

What about iron and lung cancer relation? Dust particles is always informed as one of the most important factors in increasing the risk of lung cancer. Presently, we are being able to talk about dust induced lung carcinogenesis. Some studies revealed that mineral dusts from iron can become very active especially in an aqueous medium and can form significantly high amounts of free toxic peroxy radical compounds.

Another thread like iron is cholesterol, bad cholesterol, oxidized and very oxidized low density lipoproten (bad cholesterol) in increasing cancer risk

We have got mainly two forms of cholesterol in our blood stream. Good cholesterol and bad cholesterol. Good cholesterol is also called as high density lipoprotein since it is formed by half amount of protein and half amount of lipid and the density of this structure is lower when compared with the density of bad cholesterol (low density lipoprotein). Good cholesterol is indicator of higher life quality. But, it may also be concerned as an indicator for the resistance against cancer. Because good cholesterol and its existence in blood and tissues in high concentrations above 60 mg/ml enables to bind the free cholesterol in blood stream and eliminates it by the means of urin out of metabolism. Opposite to the good cholesterol, low density lipoprotein or bad cholesterol binds the free cholesterol in blood stream onto the wall of blood vessels, other words increases the severity of atherosclerosis (vessel calcification). The details here may seem specific to cardiovascular health of individual, but in fact it is closely connected with cancer risk as well. High amount of free cholesterol on the walls of vessels, in tissue cells and in blood, means that the mechanical pressure of these cholesterol particules followed by their accumulation around cell walls may cause defects and injuries in these cell walls and may form new start points which can easily trigger cell proliferations and carcinoma formations. The same defects and injuries may form not only cholesterol and bad cholesterol but also oxidized bad cholesterol and very oxidized bad cholesterol. Of course, there are many other harmful substances like cholesterol, bad cholesterol, oxidized and very oxidized bad cholesterol which are commonly known as important factors in increasing the risk of hypertension and other cardiovascular diseases and disorders. But the mentioned substances should also be concerned importantly from the point of cancer risk. All of these harmful compounds, in case of their exaggeratedly high concentrations may accumulate beyond

cell walls and may form injuries and defects which may result in cell proliferations and carcinomas. So, what should the consumer do?. Of course the consumer can make a start by making regular check ups especially controlling bad and good cholesterol, total cholesterol and total trigliserid amounts. If the consumer carries these tests as two or three times in a year regularly, may have taken an important step in decreasing the risk of both cancer and cardiovascular diseases and disorders. The high density lipoprotein (good cholesterol) should never below 60 mg/ml, the lowest level may be 40 as minimum. If it is 40 or lower, it should beter be increased by reforming the kitchen, food and lifestyle. On the other hand, the bad cholesterol (low density lipoprotein) concentration should never exceed 120-140 mg/ml 140 mg/ml as the maximum and if the figures are higher, again the kitchen should be taken under control, withfood and life style. All the mentioned harmful substances, cholesterol, bad cholesterol, oxidized and very oxidized bad cholesterol, do not only increase the risk of cancer by only causing defects and injuries on cell walls, but they can also be converted into free toxic peroxy radial compounds(ROS). ROS may then be converted into carcinogens.

When the foods in plant origin and animal origin are compared from the point of iron content, animal origin foods appear as the richest. The reason is not only the amount of iron since there are some foods in plant origin which have got higher amounts of iron than some animal origin products. Here the criteria in evaluating the status of iron should not only be the iron amount, but also iron bioavalibility should be concerned carefullly. Because it affects the cancer potential of food even as more than the amount. The fibers such as oxalic acid, salicilic acid and phytic acid bind some of iron in the cavity of intestines and pass it directly to the feces. Therefore, the amout of iron which is absorbed through intestines and transferred into blood is directly depends on the amount of the fiber. Animal origin foods are free of fiber and they have got an extraordinary protein which carries iron and calcium through the mucosa of intestines and transferres them into blood. The same special protein carriers are not exist in plant origin foods ana thus, iron of animal origin is more absorbed and transferred into blood stream when compared with the foods in plant origin. For these reason, the

consumer should know that plant origin foods, even the richest ones in iron, should be concerned as poor sources of iron and similarly for calcium when compared with animal origin ones. This may be an advantage or a disadvantage for the consumer that depends on the target and metabolism. If the person is suffered with cancer, cancer does like iron and therefore the consumer should avoid from iron rich foods, other words animal origin foods except milk and dairy products since they are very poor in iron content. Poultry, egg and their products, red meat and its products and even fish meat and marine origin products are very rich in iron content while they are higher in iron bioavalibility. In spite of its rich iron content in high bioavalibility, fish meat should always be considered with a special and extraordinary importance in anticancer diet/ nutrition and life style because of its great antioxidants and omega 3 fatty acids which act as anticarcinogens. But, the status of the food during Marketing may suddenly change if you are free of cancer but suffered with anemia. Under such anemic conditions, a nutrition plan rich in iron content and qualit may be complementary and effective in increasing the effect of medical treatment.

What are the richest sources of iron? One parameter for the consumer, will be the origin of the food during Marketing, the animal origin foods should always be concerned as the richest ones than plant origin ones. Another parameter should be the 'color'. The darker color for both plant and animal origin foods is a strong indicator for the rich content of iron. The darker and redder the color in meat and its products including egg, polutry, red meat, their products, fish and marine origin products are, the richer the iron contents are. For this reason, the consumer can easily deduce that offals, namely liver and kidney, are rich sources of iron than a young lamb meat. Similarly, mature veal meat is richer in iron than lamb meat while turkey meat is richer in iron when compared with chicken. The rule does not change for plant origin foods that spinach is richer in iron than lettuce. Finally, one other parameter which makes animal origin foods greater is iron content and quality. Especially, the form of iron. Iron exists in nature in two forms as +2(Ferrous) and +3 values (Ferri). +2 values (ferro) form is the more quality one because it is the only form of iron which can be absorbed through the mucosa cells of intestines and transferred into blood whereas +3 values (ferri)

form can not be absorbed. Strangely, the form of iron in plants and plant origin foods is +3 (ferri) form which can not be absorbed through the mucosa cells of intestines and transferred into blood. That is why it may be clever to mix the plant and animal origin foods together during the meal preparation if the consumer is suffered with anemia. Because, this approach may increase the poor iron quality and content of plant origin food ingredients by using animal origin foods in higher quality and richer iron content. But, if the target is to be prevented from cancer, then disregard animal origin foods especially red meat and its products, egg, poultry and their products (ecxept fish ana marine!), while dominating plant origin foods such as vegetables and legumees.

FOOD	IRON (MILLIGRAMS)
Beef liver, braised (3 oz)	5.8
Lean sirloin, broiled (3 oz)	2.9
Lean ground beef, broiled (3 oz)	1.8
Skinless chicken breast, roasted dark meat (3 oz)	1.1
Skinless chicken breast, roasted white meat (3 oz)	0.9
Pork, lean, roasted (3 oz)	0.9
Salmon, canned with bone (3 oz	0.7
Fortified breakfast cereal (1 cup)*	4.5 – 18
Pumpkin seeds (1 oz)	4.2
Blackstrap molasses (1 Tablespoon)	3.5
Soybean nuts (1/2 cup)	3.5
Bran (1/2 cup)	3.0
Spinach, boiled (1/2 cup)	3.2
Red kidney beans, cooked (1/2 cup)	2.6
Prune juice (3/4 cup)	2.3
Lima beans, cooked (1/2 cup)	2.2
Tofu, firm (1/2 cup)	2.0
Enriched rice, cooked (1/2 cup)	1.4
Pretzels (1 oz)	1.2
Whole-wheat bread (1 slice)	0.9

Green beans, cooked (1/2 cup)	0.8
White bread, made with enriched flour (1 slice)	0.8
Egg yolk, large (1)	0.6
Peanut butter, chunky (2 tablespoons)	0.6
Apricots, dried (3)	0.6
Zucchini, cooked (1/2 cup)	0.3
Cranberry juice (3/4 cup)	0.3
Unenriched rice, cooked (1/2 cup)	0.2
Grapes (1/3 cup)	0.1
Egg white, large (1)	<0.1

*The amount varies.
From: The American Dietetic Association's complete food and nutrition guide, 2nd ed. 2002. USDA National Nutrient Database

The figures in the list clearly indicate that somon meat is lower in iron in spite of its high biologic value when compared with red meat. Somon and other fish meats should be participated in the anticancer diet in plenty amounts with their rich omega 3 fatty acids and some important antioxidant minerals and vitamins such as; calcium, magnesium, selenium, zinc, vitamins A, D, E, K, B complex e.g. B12, all of which are anticarcinogens.

Hormon, Food and Cancer relations with examples

Cancers including chest, prostate, ovarium, uterus and many others are closely related to hormonal imbalance, food and nutrition style and life style. A clear example to the relation of food and cancer is the comparison of the women in Europe, United States and the women in Asia and China. The incidence rate of cancer especially chest and mammary cancers in women in China and Asia seems very lower when compared with the incidence rate of the same cancers in the women in Europe and United States. The main reason for the lower incidence rate of cancers in the women in China and far east is strongly attributed to the food and nutrition style that soy and soy products including tofu, soy bean and soy milk are heavily consumed and dominated in the kitchen of far east and China. Opposite, milk and dairy products, red meat and its products and poultry and egg products are heavily consumed in the kitchen of Europe and United States. Cholesterol, bad cholesterol, trans fatty acids, omega 6 fatty acids, homocytein, saturated fatty acids and unsaturated fatty acids which may be converted into carcinogens are the main factors which result in the higher incidence rate of cancers in American and European women. On the other hand, the women and her family in Asia ana China heavily consume soy and soy products, fish and marine origin products and vegetables which supply omega 3 fatty acids, calcium, magnesium, zinc, selenium, B and C vitamins, daidzein and genistein, the substances all of which protect Asian and Chineese women from cancer. Additionally, not only the amounts and variety of carcinogen substances which may pass through the foods and nutrition style, but also the calorie intake appears as another determiner in this higher incidence rate of cancer in American and European women. Because, the higher fat and calorie intake into body increases the production rate of estrogen in both sex. The more consumption of the fat rich foods like fried ones and fast food and the less lean meat yield more fat tissue and the production rate of estrogens in body increases. The comparison of vegeterians with non vegeterians revealed

an important result that vegeterians have got lower estrogen serum levels when compared with non vegeterians. Vegeterians have got an important protein, globulin, as in higher concentration and the protein binds the excess of serum estrogen and controls it while preventing it from raising in blood serum. The persons who run a fatty and high calorie diet have got lower concentrations of globulin which may be due to the increase in fat concentration in blood serum and rationally a decrease in protein concentration including globulin in blood serum of such persons. Briefly, following a fat restricted diet in low calorie may increase the ration of globulin concentration which binds excess of estrogen while opposite may decrease the concentration of the protein and thus increase esterogen. Another adverse effect of this progress is the fattening of body as a result of the increase in esterogen since estrogen is an anabolic hormon opposite male sex hormon, testosteron. Always, the bad form of esterogen is concerned as responsible for the progress of chest and mammary cancers, but also 'fattening' should have been concerned caused by esterogen increase in metabolism. Daidzein and genistein, two anticarcinogens of soy and soy products, and omega 3 fatty acids with many other antioxidant minerals and vitamins of fish meat, may be important factors in preventing asian and far east women from cancer. But, the lower calorie of the same foods than the calorie of fatty foods and animal origin ones which are commonly consumed in Europe and United States, should be concerned as another important predisposed factor in decreasing the risk of cancer.

Saturated or unsaturated fatty acids or fats and plant origin oils are at the top of high risk foods. But, this does not mean that the consumer can consume plenty of unsaturated fatty acids. Many people trust the information on the internet and replace the animal fat with oils. Many of them concern about the beneficial effects of olive oil and other vegetable oils on body and health. Here, the comparison should be made between fats and oils not others. If we have to compare the fats and oils with other oils, it's because of their lower saturated and omega 6 fatty acid contents. But they are also lipids and they may be converted to cholesterol, saturated fatty acids and even omega-6 fatty acids in body, all of which may be converted into carcinogens. Another important reality is that there is a risk of potential cancer in the animal's

body, which is the fiber free structure. That is why the bioavailability of saturated and unsaturated fatty acids is always higher than that of plant origin because of their fiber-free structure. Even a food with a higher fat ratio may have a lower risk because of its fibers, which may decrease the bioavalibility of fats which may act as carcinogens.

According to the detailed information about hormone and food relation, the important points may be summarized as follows;

- Animal origin lipids (fats) and plant origin lipids (oils), both are harmful when they are consumed as in high quantities since excess of them can be converted into carcinogens.
- Fats are in higher risk than oils since their biologic value, to be used in carcinogenic hormones, namely prostoglandins type E2, is higher than oils. But, the most important point here is that, in spite of their higher risk and potential, oils, plant origin lipids, may also be converted into saturated fats in body and may show a higher risk to cause carcinogenic effect.

The low concentration of good cholesterol (high density lipoprotein), the high concentration of bad cholesterol (low density lipoprotein), cholesterol, high levels of serum triglyceride circulating in the blood are the main health problems reaching pandemic proportions. These factors are not only effective in the formation of obesity, cardiovascular diseases and disorders and diabetes type 2, but they may also be strong carcinogens and they may increase the formation of various cancers. Some of the specific compounds in food origin are called 'phytochemicals' which mimic estrogen in body and may be protective against all the mentioned metabolic diseases and disorders including cancer. Soy and soy products are very rich in such phtochemicals. These phytochemicals are categorized as in three classes as 'isolflavones', 'lignans' and 'coumestans'. These three groups make protection especially cancer while inhibiting tumor progress.

Isoflavones have a non-steroidal structure but possess a phenolic ring that enables them to bind the estrogen receptor and act as estrogen agonists or antagonists. This mimic prevents the binding of bad estrogen into estrogen receptors and formation of cancer.

Soybean (*Glycine max*) is composed of lipids, carbohydrates and proteins. Soybean does not contain cholesterol since it is a plant origin food. Lipids are 15 % of saturated fat, 61 % polyunsaturated fat and 24 % of monounsaturated fat. The seed contains 30 % of carbohydrates that 15 % are soluble namely sucrose, raffinose and stachyose and 15 % are insoluble. Protein content varies between 36 and 46 % (Grieshop et al 2003) whereas most of the proteins is globulin, namely glycinin and B-conglycinin. Here, the most important point is that B-conglysinin has been shown to improve serum lipid profile in both mice and human by decreasing bad cholesterol, cholesterol and serum triglycerid while increasing good cholesterol (high density lipoprotein) (Kohno et al., 2006). Soybean also contains saponins which are important anticarcinogens. The saponins in soy bean which is introduced below in detail have been shown to be anticarcinogenic by inhibiting protein kinase C activity. 'Protein kinase C (PTC)' is an ezyme which transduces the cellular signals that promote lipid hydolysis. The enzyme is activated by diacylglycerol and phospholipid. It phosphorylates a variety of proteins which control cell growth and cellular differentiation. The inhibition of the enzyme by soy bean saponins was shown in a study belong to Kim et al. (2004) to inhibit the growth of human colon cancer cells. Soy saponins also inhibit the activity of 'cyclooxygenase-2', another enzyme which is responsible for the production of inflammatory prostaglandin hormons. These hormones increase the oxidation rate and free toxic radical product concentration. Free toxic peroxy radical (ROS) increase may cause cancer since some of the free toxic radicals can be converted into carcinogenes. These harmful hormones produced by the regulation of cyclooxygenase-2 also increase TNF (Tumor necrosis Factor) which results in carcinogenic effect. On the other hand, IkBα is a polypeptide gene which inhibits NF-kB, a protein that binds to the DNA and starts the directions for the cell proliferation. Soybean saponins also alter the activity of these enzymes and inhibit cancer cell proliferation. When soybean saponins inhibit IkBα, this inhibition also decreases the activity of NF-kB and this protein can not bind to DNA and can not trigger the cell proliferation. Briefly, soy saponins may act as anticarcinogen with three mechanisms; inhibiting protein kinase C, inhibiting cyclooxygenase-2 and inhibitin IkBα and NF-kB.

SAPONINS and Cancer Relation

Saponins are a class of chemical compounds which are consist of hydrogen and carbon atoms and found in various plant species. All types of saponins derive from terpenes while terpene is formed by isoprene which is composed of five carbon atoms and eight hydrogen atoms (C_5H_8). All other terpenes are formed by this carbon hydrogen structure (isoprene). Triterpenes are terpenes which consist of six isoprene units (C_30H_{48}).

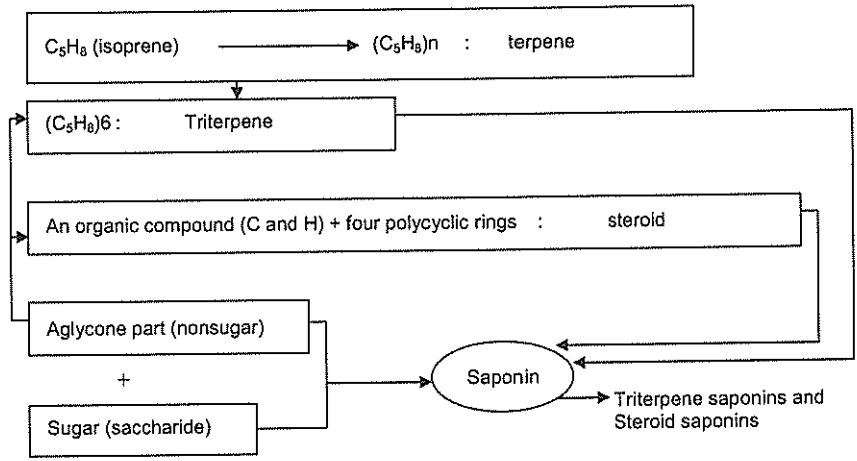


FIGURE 3

One of the most well known members of triterpene saponins, especially in sport platforms and in the elderly are *Acanthopanax* with its most well known member; Siberian Ginseng (*Acanthopanax senticosus*) is a native of the United States. It is an adaptogen that is used to relieve stress, trauma, anxiety and fatigue. The same herb is also anticholesteremic (decrease cholesterol), anti-inflammatory (reduce inflammation), antioxidant (and thus found a wide application platform in antiaging) and a nerve tonic besides its anticarcinogenic effect.

Another well known example of triterpene saponins is Soybean

(*Glycine max*), composed of lipids, carbohydrates and proteins. Soybean does not contain cholesterol since it is in plant origin.

The center of a saponin is aglycone, a non sugar part. Sometimes aglycone part may be triterpene. Triterpene is consisted of C_5H_8 (isoprene) and the number of isoprene in triterpene is 6. If triterpenes combine with sugar (saccharide), the end product is called as triterpene saponin. Sometimes aglycone part may be steroid. Steroid is an organic compound (made of C and H atoms) which contains four rings made of C and H atoms. If these steroids make combination with sugar, the end product is called as 'steroid saponins'.

'Dammarane saponins' are the saponins which have the strongest antitumor effect on various cancer types and these saponins are tetracyclic triterpenes (having more than one ring in its chemical structure). Dammaranes have got more destructive effect on cancer cells than healthy cells. They were also found as inhibitory on human breast cancer cells (MCF-7) (Qui et al 2009). They give damage to the mitochondrial membrane in both human leukemia and pancreatic cells. Mitochondria is the main energy producing organ of the cell and the cell can not survive due to the damage in its mitochondria since it can not produce energy anymore. Dammaranes, another group of saponins, cause to change in transmembrane potential, increase of calcium and destroy cancer cells (apoptosis) due to the activation in calcium transport. The richest source discovered is *Ornithogalum saudersiae* with its main antitumor substance; OSW-1 (Zhou et al 2005). Dammaranes are also found as having anticancerogen effects on breast cancer cells and NCI-H187 lung cancer cells (Phongmaykin et al. 2008), HL-60 leukemia, A 549 lung, HT-29 colon, MCF-7 breast and SK-OV-3 ovarian cancer cells (Ky et al. 2010) while Tirucallanes exhibit cytotoxity against MCF-7 cells (Chavez et al. 2005), KB epidermoid carcinoma cell lines, SK-Mel-2 melanoma, LU-1 lung adenocarcinoma and MCF7 breast cancer cells lines (Phan et al. 2014), Hela (cervical cancer cell line), A-549 (adenocarcinoma cell line), B-16(melanoma cell line), IEC-6(intestinal epitelial cell line), L-6 (myogenic skletal rat cell line) and PC-3 (prostate cancer cell line) (Rao et al. 2012).

Another saponin class, 'Oleananes' show its anticancer effect in different ways like preventing body from carcinogens in chemical

origin, boosting immun system against cancer cells and killing cancer cells. Avicins (a cactus plant; *Acacia victoriae*) can alter the structure of Stat 3. Stat 3 gene is a member of the family known as Statgenes. These genes provide instructions for making proteins that make vitaly important functions in essential chemical signaling pathways within cell. When Stat genes and their proteins are activated by chemical signals, they move into nucleus in cell and attach DNA (genom of the cell). This integration of Stat genes with DNA initiates the cell proliferation since the coding system is changed by STAT genes in DNA. Therefore, the alteration of Stat genes by avicin saponins and the destruction of these proteins by the avicin saponins may inhibit cell proliferation since many Stat genes due to the destruction can not enter into cell, and integrate with DNA and thus can not induce cell proliferation. As a result, cell proliferation may be inhibited which may be a strong inhibitory factor on tumorogenesis (Haridas et al. 2009).

HeLa cells are the human epithelial cervical cancer cells (upper region of vagina in female urogenital system) which can be destroyed by another saponin class; 'Tubeimoside' (from the bulb of *Bolbostemma paniculatum Franquet*) due to its destructive effect on endoplasmic reticulum (the organ of the cell which is responsible for the synthesis of proteins and lipids of the cell) (Haridas et al. 2009). Followed by destructive effect of Tubeimoside saponins on endoplasmic reticulum, cancer cell can not produce proteins and lipids for the cell, can not recover its wounds and can not proliferate. The result is the inhibition of cancer cell growth.

MMP-2 and MMP-9 (metalloproteinase-2 and 9) are the enzymes consisted of metals and proteins which are the combinations in harmful potential that may be carcinogenic. The productions of MMP-2 and MMP-9 are suppressed by soybean saponins. Such metalloproteinase compounds increase the risk of tumorogenesis since they decompose metalloproteins which make metals free and activated. Especially, a similar important metalloproteinase in soy products called TIM-2 (Tissue Inhibitor of Metalloproteinase) inhibits MMP-2 and MMP-9 and may decrease the risk of tumorogenesis due to carcinogen metals (Kang et al 2008).

Formosanin C (which is present dominantly in *Rhizoma paris*) is

another saponin in antitumor effect on MH134 mouse hepatoma cells by some modifications of the immun system. The working mechanism is based on its immunostaining effect (Wu et al. 1990). These chemical compounds show lipophilic (fat loving) and hydrophilic (water loving) attributes. These attributes are important from the point of view of health since they can bind water and fat in water, decrease water binding capacity and hence eliminate toxic substances with water excreation. They also reduce cholesterol, bad cholesterol and serum tryglyceride by their ability to bind fat and fat like substances, which are the primary causes of cardiovascular diseases and disorders and which may be converted into carcinogens. A most common example is digoxin, which is commonly used as a drug for cardiovascular diseases and disorders. Gauthier et al., 2009), which has been reported to be involved in the production of cholesterol bound saponins in cell membranes (Melzig et al., 2001). This property may be one of the mechanisms of the anticancer effect of saponins although it is not clearly understood and thus, needs further studies to be highlighted.

Saponins bind the excess of cholesterol and bile salts in the cavity of intestines and therefore decrease their absorption level through the mucosa of intestines. The decrease of cholesterol, bad cholesterol, bile salts and trigliserids in intestinal cavity may prevent the body from convertion of the mentioned substances into carcinogens while decreasing their concentraions in blood and the risk of cardiovascular diseases. Thus, saponins are very effective in prevention from both cancer and cardiovascular diseases.

Saponins are commonly exist in various plants, in roots, tubers, leaves, blooms and seeds. These pyhtochemicals are shown to have antitumor effect on many types of cancer cells upto 0.2 mM. If the glycosyl part combines with a carbon and hydrogen body (C_30H_{48}), such saponins are called as triterpen saponins. If the concerned saponin's glycosyl part makes combination with a steroid, an organic compound that contains a specific arrangement of four cycloalkane (the rings of carbon atoms) rings form and they are called as steroid saponins which are also indicated above. The steroidal saponins are found in Agavaceae (a subfamily of monocot flowering plants in family *Asparagaceae,* namely Joshua tree), *Dioscoreaceae* (a family of plants which are

monocotyledons, other words the plants of the family contains one seed-leaf, a well known example is Yam (*Dioscorea*), *Liliaceae* (the member of this family have linear leaves which like sunny climates and many of them are poisonous if eaten and may cause serious toxications in body, *Solanaceae* (a family that contains many important crops as well as toxic ones which includes chili pepper, potato, tomato, eggplant and tobacco), *Scrophulariaceae*, *Amaryllidaceae*, *Leguminosae* (a well known group in public consumption with its well known examples; *Glycine max*: soybean, *Pisum sativum*: pea, *Cicer arietinum*: chickpeas and phaseolus: beans, *Arachis hypogaea*: peanut, *Ceratonia siliqua*: carob; *Glycyrrhiza glabra*: licorice, *Medicago sativa*: alfaalfa and *Pueraria lobata*: kudzu), *Rhamnaceae* (most of the family is berry while some members are nuts). Asparagus saponins (101.15 mg/L at 72h) inhibits the growth of human hepatoma cells, HepG2, by activating the pro-apoptotic caspase-9 and caspase-3, decreasing the mitochondrial membrane potential, increasing intracellular ROS and Ca^{2+} and the overexpression of apoptotic proteins, Bcl2 and Bax (Ji et al. 2012).

The type the saponin may be an important factor in determining the anticancer status of the food on cancer that only one detailed research from a few ones, observes more anticancer effect in monosaccharide analogues rather than the disaccharide form (Kaskiw et al. 2009).

One of the triterpene saponins is *Acanthopanax*. The most commonly known member in the family is Siberian Ginseng: *Acanthopanax senticosus,* which is native to Northeastern Asia and the herb is adaptogen that is used to relieve stress, trauma, anxiety and fatigue, anticholesteremic, anti-inflammatory, antioxidant and a nerve tonic that acts therapeutically upon the nerves and serves to calm ruffled nerves). The others are *Leguminosae*, *Araliaceae*, *Scrophulariaceae* (commonly found in temperate areas and tropical mountains), *Campanulaceae* and *Caryophyllaceae* (which includes ornamental plants, widespread in Mediterranean and bordering regions of Europe and Asia). There are many classes of Saponins but the classes; *dammaranes*, *oleananes*, *lupanes* and *steroids* are the ones which have got stronger antitumor effect on cancers. The saponins in Ginseng radix was also found inhibitory on human pulmonary adenocarcinoma cells (Lee et al. 1999). Saponins, the major family of secondary metabolites containing a sugar

moiety glycosidically linked to a hydrophobic a glycone that allow its fat-soluble character besides being water-soluble (due to the sugar moiety) are exist in richest amounts in yucea, christmas rose (*Helleborus niger*), horse chestnuts (*Aesculus hippcastanum*), asparagus fern (*Asparagus officinalis*), daisies (*Bellis perennis*), chickpeas, soybeans (Kerwin 2004), chickpea (Serventi et al. 2013, Carlson et al. 2009), alfaalfa (Gurfinkel and Rao 2003), *Moringa oleifera Lam.* (Sharma and Paliwa 2013), Trigonella foenum graecum (fenugreek) (Arivalagan et al. 2013), *Gymnema sylvestre* and *Eclipta prostrata* (Gopiesh and Krishnan 2009). The second mechanism for the anticancer effect of Saponins is due to their bile acid binding ability. Some bacteria in the large intestine turn primary bile into a substance that is highly carcinogenic which is also the main reason for the increase in cancer risk with high fat diets. Modification of bile acids by gut bacteria has the potential to be involved in the pathogenesis of colorectal cancer. These bile acid end products formed due to bacterial flora in colon have pro-inflammatory and anti-apoptotic effects which facilitate the survival of malignant cells while increasing the rate of DNA damage accompanied by a high fat diet. Similarly, the bile acid and bile acid by products show the cancerogen effect also in esophagus, stomach, pancreas, the small intestine besides colon (Bernstein et al. 2005). The diets rich in meat and low in fiber such as saponins besides fat rich diets such as saponins fat rich diets increase the delivery of proteinaceous residues which promote proteolytic fermentation with the production of ammoniac compounds and branched chain fatty acids which are inflammatory and may enhance the risk of colon cancer (Waldecker et al. 2008; Windey et al. 2012). Around 400-800 mg of conjugated bile acids which are formed solely by a broad spectrum of intestinal bacteria with their bile-salt modifying gene coded enzymes (Ridlon et al. 2006) reach the colon without any trace of them in feces since a great portion enter the systemic circulation as being not sequestered by the liver (Thomas et al. 2008) and can accumulate to high levels in the enterohepatic circulation of some individulas. Hence, they may contribute to the formation of colon cancer and gallstones (Ridlon et al. 2006). The conjugated bile acids are converted to free primary bile acids namely deconjugated cholic acid, chenodeoxycholic acid and amino acids (Begley et al. 2005;

Ridlon et al. 2006). Finally, the primary bile acids are modified by the gut microbiota, generating the secondary and tertiary forms of bile acids through dehydroxylation, dehydrogenation and sulphation which are claimed to be the primary reasons of a wide range of human diseases including cancer (Matsuzaki et al. 2013; O'Keefe 2008; Huycke and Gaskins 2004). On the other hand, confirming the metioned findings, increased fat and carbohydrate is often linked with colon and colorectal cancer since it elevates the rate of bile secretion (Degirolamo et al. 2011; Suzuki et al. 2014; Xu et al. 1999 and Shin et al. 2013). As clearly supported by the findings related to the bile salt binding ability of saponins, especially during or followed by the high fat or carbohydrate diets which elevate bile acid levels, saponins may decrease the risk of colon, colorectal and some other cancers.

Soy saponins were claimed to cause apoptosis on HT-29 human Cancer cells by increasing the activity of AP, a transcription factor which regulates gene expression, in response to a variety of stimuli including cytokines, growth factors, stress and infections while reducing the activity of PKC (a family of serine-threonine kinase enzymes) which acts as a tumor promoter (Tsai et al. 2010). 140 g daily intake of soy saponins as the highest quartile (0.89, 0.51-1.54, 95% CI) versus 49.7 g daily intake (as the lowest quartile(R: 1.00, 95% CI) in men and 126.9 g daily intake of soy saponins (as the highest quartile (0.49, 0.23-1.07, 95% CI) versus 46.7 g daily intake (as the lowest quartile (R: 1.00, 95% CI) was informed to decrease the risk of death from stomach cancer by Nagata et al. (2002). Their study from 30304 men and women with 35 years of median age of 7 years was smoking and alcohol adjusted. ≥28.2 g daily intake of saponins as the highest quartile (0.89, 0.80-0.99, 95% CI) versus <6.4 g of daily intake as the lowest quartile (R: 1.00, 95% CI) reduced the risk of prostate cancer. The follow up of this study carried our by Park et al. (2008) was 8 years including 82.483 men and 4404 prostate cancers. The study was smoking adjusted while alcohol not. Similarly, peanut saponins as in 2 meals a week as the highest quartile (0.83, 0.50-1.37, 95% CI) versus no peanut consumption (R:1.00, 95%) in men and 2 peanut meals a week as the highest quartile (0.75, 0.40-1.43, 95% CI) versus no peanut consumption in women decreased the risk of colorectal cancer (Yeh et al. 2006).

One of the new saponins, isolated from the seed kernels of *Entada phaseoloides* (Linn.) *Merr.* showed its anti-cancer effect on esophageal carcinoma via the same mechanisms, increasing the activities of caspase-3 and -9, reducing Bcl-2 and Bax, the anti-apoptotic proteins, and finally increasing the generation of free oxygen reactive species (Ma et al. 2013). One of the most important points about the association of saponins and cancer is the destruction of cancer cells by reactive oxygen species which are produced by saponins. This detail appears as one of the evidences for the cancer destroying effect of reactive oxygen species, though the same compounds increase the risk of cancer in healthy individuals. One of the soy saponins has been shown to have anti-cancer effect on human colon cancer cells, HT-29, by suppressing the activity of PKC (a family of protein kinase enzymes that control the function of some proteins through the phosphoylation of serine and threonine) without any effect on p53 (tumor suppressor protein) (Tsai et al. 2010).

TTB2, a steroidal saponin which is isolated from the rhizomes of *Tschonoskii maxim*, has anti-cancer effect on A549 lung cancer cells, causing loss of mitochondrial membrane potential, cell cycle arrest (in the G2/M phases) and finally, the increase in the level of ROS (Huang and Zou 2011). Similarly, α-hederin, a monodesmosidic triterpenoid saponin, distributed in Hedera or Nigella species, namely *Clematis ganpiniana*, has its anti-cancer effect on breast cancer cells by promoting caspase-3 and caspase-9 activation, inducing depolarization of mitochondrial membrane potential which releases Apaf-1(a protein which acts for the downstream of p53, tumor suppressor protein) and cytochrome c, a small hemeprotein, which is found as associated with the inner membrane of mitochondria. Its release from the inner mitochondrial membrane activates the apoptosome, the protein globules, which contributes to cell death. Finally, this saponin, like many other saponins, destroy cancer cells by inducing the generation of reactive oxygen species (Cheng et al. 2014).

Saponins have antibacterial effects and hence, they support the immun system, allowing a better defence of the immune system on cancer cells. The factor of 'bacteria' should often be taken into consideration in the progress of some types of cancer. Because they

induce chronic inflammation and produce carcinogenic bacterial metabolites namely fecapentaenes, the potent in vitro mutagens, mutagenic free radicals, N-nitroso compounds and bile salt metabolites which may cause cancer like in the case of the strong link between *Helicobacter pylori* and adenocarcinoma (Parsonnet 1995). On the other hand, the association of some bacteria with cancer appears for not all types, but for some cancer types. Because, the bacteria may even be a promising carrier of therapeutic agents for melanoma, colon and bladder cancers while having promoting effects on gallbladder cancer, like in the case of *Salmonella typhii*. Similarly *Helicobacter pylori* as one of the primary reasons of gastric cancer may reduce the risk of esophegal cancer in some individuals. Bacteria may cure or cause remission of some of the cancers by colonization or stimulating immune responce via its infection against cancer, or some of their toxins, like the 'Coley's vaccine' which was succesfully administered by Dr. William Coley by using *Streptococcus pyogenes* against sarcoma, melanoma, myeloma and lymphoma (Zacharski and Sukhatme 2005; Mager 2006), or increasing plasma ghrelin leading to increased appetite and weight gain like in the case of *Helicobacter pylori* (Grimley et al. 1999). But, many bacteria species may link to cancer pathogenesis by inducing inflammation and carcinogenic metabolites. Confirming the relation between some pathogens and their association with some cancers and anticancer effect of saponins against these pathogens which cause cancer, saponins with their antibacterial effects against *Staphylococcus aureus*, *Aspergillus flavus*, *Aspergillus niger* (Khanna and Kannabiran 2008), *Salmonella typhi* (Evans et al. 2002 and *Helicobacter pylori* (Bae et al. 2003), saponins may have a clear anticancerogen effect on some types of these cancers in bacteria origin. Besides the mechanisms about the anticancerogen effects of saponins, they may show this effect by overexpressing PROX1 and 6 (the homebox genes which give rise to the mammalian lymphatic system), blocking the elevation in the Reactive Oxygen Species (ROS), through cell cycle arrest, by activating the mitochobdrial signal pathway, by increasing the levels of caspase-3, 9 (the members of the cysteine-aspartic acid protease, caspase and cytochrome C protein (a small hemeprotein in the inner membrane of the mitochondrion), by suppressing protein kinases of VEGFR 2(one of

the phosphoylase receptors of tyrosine kinase), by increasing P38MAPK (an activated protein kinase which is responsive to stress stimuli such as cytokines, ultraviolet irradiation heat p53 and osmotic shock), by overexpressing CDK2 and cyclin A (the proteins which regulates cell division) and DNA topo 1(the enzymes that regulate the overwinding or underwinding of DNA). These mechanisms related to the anticancer effect of saponins were observed also in some recent studies in esophageal cancer cell line Kyse510 (Wang et al. 2012), adenocarcinomic human epithelial cell line A549, H1299 human lung carcinoma cell line (Ming-Ju et al. 2013) and HL60 human promyelocytic leukemia cells (Zhiyu et al. 2012).

Cycloartane saponins ($C_{30}H_{52}$), for example, *Astragalus* saponins have antitumor properties in human colon cancer cells. These saponins down regulate the expression of the human colon cancer tumor market alpha fetoproteins and suppress HepG2 (colon cancer cells) growth by inducing apoptosis (self killing of cancer cells). The plant, *Astragalus* has been widely used in Chinese medicine. Especially, the root of the plant may be consumed by preparing its tea while it can be found in market as in extract tablet form or capsule. In case of its use as combined with *Ginseng, licorice* and *Angelica*, the antitumor effect because of the additional anticarcinogen saponins coming from Ginseng, Licorice and Angelica, may increase the antitumor potential of the tea that is prepared. But, this plant should not be used during the treatment with anticancer treatments with drugs (as an example, during the treatment with cuclophosphamide) or before, during and after organ transplants because of some contraindications among the mentioned medications. Another saponin group called as Saikosaponins alter the transcription of human liver cancer cells (HepG2) and therefore inhibit their growth. *Ganoderma applanatum* and curcumin are the plants which are the richest in Saikosaponins.

The main beneficial effect of saponins besides anticarcinogenic effect takes its origin from its lipophilic (fat loving) and hydrophilic (water loving) attributes and they can bind both water and fat in blood, decrease water binding capacity and eliminate toxic substances out of body. Excess of saturated fat in blood can be bound by saponins with their lipophilic attribute. Cholesterol, bad cholesterol, oxidized bad

cholesterol, saturated fat, unsaturated fat and trans fats, can be bound by them due to their lipophilic characters. The decrease of cholesterol and its other forms in blood, in addition to the binding of saturated, unsaturated and trans fats by saponins, may not only protect from cardiovascular diseases and disorders. They can also protect from cancer.

Saponins may have anticarcinogenic effect in three ways. One of them is their cholesterol-like compund binding ability that cancer cells have a different membrane structure with a more cholesterol-like compound concentration, like in monoblastoid lymphoma cell line U937 which was shown as 30-fold more sensitive to killing and growth inhibiting by saponins (Hu et al. 2010). On the other hand, saponins can show the cholesterol binding ability with glutamic acid, glisin and valin ((GLU-188, GLN-119, VAL-72 and GLN-71) (Singh and Shukla 2012). Confirming the anticancerogenic effect of saponins via the binding cholesterol, avicins, a class of natural saponins from acacia, with selective pro-apoptotic activity in cancer cells, accelerates hydroperoxide-induced oxidation of mitochondrial endogenous NAD(P)H, a cofactor, which is a non protein chemical compound and used in anabolic reactions like lipid and nucleic acid synthesis. The accelerated oxidation of NAD(P)H results in the drop of the inner membrane potential and the high amplitude swelling of mitochondria, as a result, the ROS and cytochrome c release and apoptosis followed by the binding of avicins to cholesterol in the cell membrane of cancer cell (Lemeshko et al. 2006; Hanausek et al. 2001).

When it comes to the steroidal saponins they are namely;

- Agavaceae (a subfamily of monocot flowering plants in the family *Asparagaceae*, namely Joshua tree)
- *Dioscoreaceae* (a family of plants which are monocotyledones, other words, the plants of the family contains one seed-leaf with a well known example, Yam (*Dioscorea*)
- Liliaceae (the members of the family have linear leaves that like sunny climates and many of them are poisonous if eaten and may cause serious toxications in body. One of the example from the family is *Solanaceae* that this family contains many important

crops as well as toxic ones which includes chili pepper, potato, tomato, eggplant and tobacco.

- *Leguminosae* (a well known group in public consumption with its well known examples; *Glysine max* (soybean), *Pisum sativum* (pea), *Cicer arietinum* (chick pea) and *Phaseolus* (beans), *Arachis hypogaea* (peanut), *Ceratonia siliqua* (carob), *Glycyrrhiza glabra* (licorice), *Medicago sativa* (alfaalfa),
- *Rhamnaceae* (the well known members of the family are berry and nuts)

Licorice is mainly known in Chinese herbal medicine which is called 'Gan-Cao', a traditional chinese herbal. Especially, the dried roots and rhizomes of *Glycyrrhiza uralensis*, *G. glabra* and *G. inflata* is used as complementary to the medical treatment. The functional medical components of licorice are mainly two as saponins and various types of flavonoids (Zhang and Ye, 2009). The extracts of the plant with its flavonoids show antibacterial effect to *Helicobacter pylori*, the causative agent of peptic ulser. The namely flavonoids that inhibit the bacteria in the plant are; glabridin, glabrebe (components of *Glycyrrhiza glabra*), licochalcone A(*G. inflata*), licoricidine and licoisoflavone B (*G. uralensis*) (Fukai et al. 2002).

Licorice with its rich saponin and flavonoid contents, especially with its most commonly known flavonoid 'glycyrrhizin' has gained extensive use in foods, tobacco and in both herbal and traditional medicine. The consumption has reached upto such a huge level that today licorice and glycyrrhizin in only the US is estimated as between 0.027-3.6 microgram per Kg daily. Glycyrrhizinates inhibit 11 beta hydroxyesteroid dehydrogenase, the enzyme responsible for inactivating cortisol. Thus, high level of licorice consumption in the long run may produce hypermineralocorticoid- like effects in both animal and human. Fortunately, 0.015-0.229 microgram glycyrrhizin per Kg of body weight daily, other words, the consumption limits for today has been proven as non toxic and free of side effects (Isbrucker and Burdock 2006). Glycyrrhizin serves as also the initial anticancer agent of the plant that it was shown to inhibit rat liver carcinogen metabolizing enzymes while boosting testosteron production (Paolini et al. 1999). Glycyrrhizin

is mostly rich in the root of the plant and it is a triterpenoid saponin while it has an additional liver protecting effect and antiviral (protects against viral infections). It stimulates the antiinflammatory effects of glucocorticoids, increases interferon levels and augments natural killer cell activity. Glycyrrhetic acid, the biologically active metabolite of glycyrrhizic acid is 200 to 1000 times more potent inhibitor of 11 beta hydroxystenoid dehydrogenase than glycyrrhizic acid. Otherword, Glycyrrhetic acid may even be more cortisol activating part of licorice. Isoflavones from *Glycyrrhiza glabra* have been shown to protect mitochondria (energy producing organs of cells) from oxidative damage. Licorice also inhibits low density lipoprotein (bad cholesterol) oxidation. Finally, Glabridin, the major isoflavon in the root, binds to the receptor in the cell before binding of harmful estrogen which is one of the main reasons for chest and mammary cancer prevention by the isoflavon. All these details about licorice may be the main reasons for the plant which makes it one of the most effective and beneficial plants in cancer diet and kitchen. The plant compounds also raise interferon and therefore protect against cancer and inflammation while boosting immun system. Not only the patients with cancer, but also the healthy ones can be protected from hypertension, calcification and oxidative stress with licorice (Jamison 2003).

One of the fewest fruits in the world which is one of the richest in saponins is bitter melon (*Momardica charantia*). The fruit contains a variety of potentially bioactive compounds which are saponins with the most common one; cucurbitane and oleanane-type triterpenoids. The mentioned saponins of the fruit was found as inhibitory on a group of adipose (fat) tissue which accumulates fat and contribute to the increase in cancer risk. These cells (3T3-L1) are inhibited and their proliferation rate decreases by bitter melon saponins and the fat accumulation and thus fattening rate decreases (Popovich et al 2010). This function of the fruit may be helpful and beneficial for the person with the cancer or a healthy person since excess of fat tissue is always a great contributer to cancer because of the conversion of oxidized fats to carcinogenes (toxic radicals).

The anticancer effect of many of the chemicals which are naturally exist in plants have been proven by many studies. Flavonoids (or bioflavonoids) as a separate class of these phytochemicals are the plant secondary metabolites. First, they were referred to as vitamin for permeability, vitamin P, because of their effect on the permeability of vascular capillaries, but the term has fallen out of use since 1950s (Benthsath et al. 1937). The word, flavon, comes from the latin word 'flavus' which means yellow, the colour of them in nature. The molecular structure of flavonoids is 2-phenyl-1, 4-benzopyrone and 3-phenyl-1,4-benzopyrone for isoflavonoids which are derived from flavonoids. Pterostilbene in grapes and blueberries has an apoptotic and anticancer effect on DU145 human prostate, T24 and HT1376 human bladder, SK-Mel-28 melanoma (Kim et al. 2009; Kuo et al. 2008 and Larrosa et al. 2004). Piceata

Estradiol, the female hormone in vertebrae, refers to the 17-beta-isomer of estradiol, an aromatized C_{18} steroid with hydroxyl group at 3-beta-positions with the molecular formula $C_{18}H_{24}O_2$. Estradiol-17-beta is the most potent form of mammalian estrogenic steroids. It is produced by the cyclic ovaries, the placenta, the adipose tissue of men and postmenopausal women. The 17-alpha isomer of estradiol, opposite to Estradiol-17-beta binds to estrogen receptors weakly and exhibits a lower rate of estrogenic activity in estrogen responsive tissues. Therefore, phenyl-benzopyrene, C18 aromatizad isoflavonoids in plant tissues and estrogen in mammalian tissues are cery close in their chemical structures and both are benzopyrone, C_{18} aromatized phenolic compounds. Isoflavones constitute the largest group of natural isoflavonoids which are exist in plants (Boland and Donnelly 1998). Because of the mentined similarity which is also reflected to their functions, isoflavones are often considered as phytoestrogens which mimic estrogen in body. They keep estrogen levels under control as they can act like a weak estrogen when body estrogen levels are low and can inhibit estrogen's effect when body estrogen levels are high (Wiseman et al. 2000). The increase in the risk of certain cancers such as breast and

prostate by the female hormone, estrogen, is well established (Nichols et al. 2013).

Prostate cancer is the second most frequent cause of cancer and the sixth leading cause of cancer death among worldwide (Ferlay et al. 2010; Center et al. 2012). The main cause in the progress of prostate cancer is the androgen dependent physiological development of prostate. The high affinity androgen receptor ligand 5α-dihydrotestosterone (DHT) as the receptors of the main androgen is involved in the development of prostate cancer. Especially 5 α-androstane-3 alpha, 17beta-diol reduced from 5 α-DHT and its activated signaling may be one of the pathwways responsible for the progression to androgen-independent prostate cancer (Yang et al. 2008). Testosteron is converted to 5alpha-DHT by the enzyme Delta(4), 3 ketosteroid, 5alpha-reductase in prostatic stromal and basal cells. DHT is primarly responsible for prostate development and the pathogenesis of benign prostatic hyperplasia. Inhibitors of 5alpha-reductase reduce prostate size by 20 % to 30 %, accompanied by the induction of apoptosis, reduction in VEGF and as a result, vascularization (Steers 2001; Rittmaster 2011). The marked dependency of prostate carcinogenesis on androgens, unfortunately, leads to metastatic castration-resistant prostate cancer (CRPC) unless it is remedied by surgical resection or radiation therapy. The first 3 year period is crucial in the treatment of the cancer before it turns to incurable CRPC (Knudsen and Scher 2009).

The therapies using the inhibition of androgen with GnRH (Gonadotropin-releasing hormone, the trophic peptide hormone responsible for the release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) from the anterior pituitary and released from neurons within the hypothalamus) agonists or blockage of the androgen receptor with high affinity agents lead to mutations or deregulation of these receptors (Knudsen and Penning 2010). The mutations of the androgen receptors results with the high abundance of androgen receptor molecules. Hence, the receptor activation may occur in spite of a limited number of androgenic ligand. Briefly, the therapies (including the androgen inhibitors; abiraterone acetate and MDV3100)) which are used to inhibit or blockage androgen receptors, may cause a resistance of these receptors by mutating them, pending the expected anticancer

effect of therapy during the treatment period (Walttering et al. 2012; Sadar 2011). On the other hand, estrogen receptors α and β have been identified with their opposite effects that the estrogen receptor- α is the mediator of inflammation and malignant pathologies whereas the estrogen receptor- β is anti-proliferative and antiinflammatory (Ali and Coombes 2000; Giulianelli et al. 2012; Murphy and Leygue 2012 and Ström et al. 2004).

Phytoestrogens may have an anticancer effect in hormone dependent cancers such as breast and prostate cancers by stimulating and increasing the activity of estrogen receptor β which is anticancer and antiproliferative or by inhibiting estrogen receptor α which is proliferative, inflammatory and cancerogen (Thelen et al. 2014). But, this effect may be weaker in some phytoestrogens. The current data supports the anticancer effect of phytoestrogens namely genistein, daidzein, biochanin A and resveratrol with their stimulating effect on estrgen receptor β but claims the same effect as weaker in equol, naringenin and kaempferol (Harris et al. 2005; An et al. 2001). Confirming these results, genistein was informed to block 5alpha-reductase-2 gene expression and subsequently inhibits prostate growth which is stimulated by a high dietary fat intake as a great risk factor for prostate cancer (Zhu and Sun 2005).

The necessity of phytochemical containing foods in cancer nutrition with their beneficial effects on serum lipids associated with cardiovascular health, decrease in the risk of osteoporosis by enhancing Ca absorption and binding capacity and relief of menopausal symptoms besides cancer chemopreventions (Singh et al. 2010) appears as vitally important. Thus, all phytochemicals with their anticancer and other beneficial effects should have been carefully concerned during the creation of cancer nutrition. One group of phytochemicals having got important anticancerogenic effect is 'natural monophenols', consisting of a hydroxyl group (-OH), bonded directly to an aromatic hydrocarbon group. The widely known natural monophenols are Apiole with its richest sources, parsley and dill (Atta-Aly 1999, Bailer et al. 2001) and Carnosol with its richest sources, rosemary (Jordan et al. and Johnson 2011).

The other group of phytochemicals in phenolic structure is polyphenols, characterized by the presence of large multiples of

phenol structural units. The number and characteristics of the phenols determine the physical, chemical and biological properties. Tannic acid with its natural sources; sorghum, millet, barley, rice, wheat, corn, soybean, legumes (Chung et al. 1998), grapes, cranberries, strawberries, blueberries (Kim et al. 2010; Vattem et al. 2005; Puupponen-Pimia et al. 2001) and Ellagitannins with its sources; strawberry and pomegranate (Starma et al. 2010) are the two widely known polyphenols. The third group of phenolic phytochemicals, flavonoids, is the widest group which is consisted of 'Flavonols' (3-hydroxy-2-phenylchromen-4-one), namely quercetin with its richest sources; onion, apple, cranberries, buckwheat (Jin et al. 2011; Reay and Lancaster 2001; Neto 2007; Lee et al. 2013 and Plumb et al. 1999).

'Isoflavonoids' is another group of phytochemicals that is consisted of isoflavones (phytoestrogens), isoflavanes, isoflavandiols, isoflavanes, pterocarpans or coumestans (phytoestrogens) and coumestrol. Isoflavones comprise a class of organic compounds and mimic estrogen of mammals. The antioxidant potency of soy isoflavones genistein and daidzein were found to be much weaker in their glycoside (as bound to another functional group via a glycosidic bond) forms when compared with their aglycone (the compound remaining after replacement of the glycosyl group from a glycoside by a hydrogen atom) forms (Lee et al. 2005). Thus, glycation, the binding of sugar molecule to either a protein or lipid molecule without an enzyme, seems an important criteria that determines the anticancer potential of phytochemicals, especially phytoestrogens. The most commonly known glycation is the Maillard reaction, the glycation of sugar to protein and the reaction is triggered by heat and water. Therefore, processed foods that require heat and cooked foods which require water may always lead to some level of glycation which may result in antioxidant potency of phytochemical in food. The findings of Lee et al. (2005) underlines the importance of nonprocessed fruit and vegetable consumption rather than processed while limiting processed carbohydrates and browned foods. The existence of the Advanced Glycation End products (AGE) in high concentrations in various human cancer tissues indicates a strong association between AGEs and cancer (van Heijst et al. 2005; Ansari and Rasheed 2010; Takino et al. 2010; Shimomoto et al. 2012). Not only the AGEs but also

the Receptor for Advanced Glycation End-products (RAGE) play a key role in several diseases including diabetes, arthritis, Alzheimer's disease and cancer. RAGE ligands, S100/calgranulis (low-molecular-weight calcium binding proteins found in vertebrates) and high-mobility group box 1 (HMGB1) (a protein secreted by activated immune cells such as macrophages and monocytes) are expressed and secreted by cancer cells and are associated with increased metastasis. They can influence tumor microenvironment including fibroblasts, leukocytes and vascular cell, leading to increased fibrosis, inflammation and angiogenesis (Logston et al. 2007). Therefore, the consumption of glycated foods during cancer can elevate the RAGE secretion by cancer cells, increasing the level of inflammation, fibrosis and angiogenesis. So, the interaction between AGEs and RAGE and their stimulating effect on each other (Rojas et al. 2010) which may stem from nutrition rich in glycated foods increase cancer progression.

Isoflavanes (3-phenylchroman) are consisted of lonchocarpane and laxiflorene (Cassidy and Setzer 2011) (with their sources; *Anacamptis* and *Lonchocarpus laxiflorus*). Coumestans, another namely isoflavonoids, are the oxidation products of pterocarpans (derivatives of isoflavonoids) in benzo-pyrano-furano-benzene structure, with its sources, orange juice, orange, milk, broccoli, beans and refined bread (Carmichael et al. 2011).

Silymarin is one of the most commonly known flavonolignan (another group of phytochemicals, natural phenols like the phytochemicals above but composed of a part of flavonoid and a part of lignin), which has a strong antioxidant and anti-hepatocellular carcinoma activity, with its richest sources arthicoke and milk thistle (Fereira et al. 2013; Podder et al. 2012).

Another group of phytochemicals are phytoestrogens in a polyphenolic structure with their antioxidant effect and dibenzylbutane skleton. Flax seed and sesame seed contain higher levels of lignans (sesamin) than most of other foods (Ide et al. 2003; Liu et al. 2006; Lim et al. 2007; Gerstenmeyer et al. 2013) which are known as the richest sources of lignans like rye, aot and barley (Bartkiene et al. 2012). Secoisolariciresinol and pinoresinolare are the other lignans in

sunflower seeds and pumpkin (Zaineddin et al. 2012; Sicilia et al. 2003 and Wikul et al. 2012).

Stilbenoids are hydroxylated derivatives of stilbene (1,2-diphenylethene). The most common known stilbenoid is resveratrol, a natural polyphenol in grapes with anti-inflammatory, anti-platelet, anti-fungal, anti-bacterial, antioxidant, phyto-estrogenic, cardioprotective and anti-cancer effects (Kucinska et al. 2014; Aggarwal et al. 2004; Piotrowska et al. 2012 ; Jang et al. 1997 and Fouad et al. 2013). The other stilbenoid is pterostilbene and piceatannol in grapes and blueberries which are chemically related to resveratrol (Bavaresco et al. 2002 and Kim et al. 2008).

Curcuminoids are the natural phenolic phytochemicals in a linear diarylheptanoid structure with curcumin or its derivatives and different chemical groups which increase solubility of curcuminoids and make them suitable for anti-cancer drug formulations. Turmeric and mustard are the richest sources which have their own yellow color given by curcumin (Martin et al. 2012; Anand et al. 2008 and Tayyem et al. 2006).

Tannins are the polyphenolic compounds that contain a carbohydrate and hydroxyl group with an esterified phenolic group such as gallotannins or ellagic acid in ellagitannins. The hydrolysable ones yields gallic or ellagic acids when heated with an organic acid. Ellagitannins namely rich foods are pomegranate (Heber et al. 2007; Vrhovsek et al. 2012), strawberry, raspberries, cloudberries in addition to another important tannin with its rich sources pomegranate and green tea (Carreras et al. 2012 and Adams et al. 2006).

Aromatic acid is another phenolic phytochemical which contains an aromatic ring with an organic acid namely phenolic acid, salicylic acid, vanillin, gallic acid, ellagic acid and tannic acid and additionally hydrocinnamic acids, namely cinnamic acid, chlorogenic acid, coumaric acid, caffeic acid, cichoric acid and α-cyano-4-hydroxycinnamic acid with their rich sources; coffee (caffeic acid) (Kang et al), *Echinacea purpurea* (cichoric acid) (Wills and Stuart 2000), egg plant (ferulic acid)(Manach et al. 2004), canola, rapeseed and *Brassica juncea* (Indian mustard) (sinapic acid) (Khattab et al. 2010), *Syzygium alternifolium* (cinnamic acid) (Kasetti et al. 2012), coffee (chlorogenic acid) (Suarez-Quiroz et

al. 2014), peanuts, tomatoes, carrots, garlic, vinegar (coumaric acid) (Stojkovic et al. 2013), chokeberry, blueberry, Saskatoon berry, dark plum, cherry, apple, coffee and tea (phenolic acids) (Mattila et al. 2006), strawberry, Sichuan pepper, basils (α-cyano-4-hyydroxycinnamic acid) (Vina et al. 2003), apple, banana, lemon, nectarines, plum, grape, grapefruit, tomato, carrot and cucumber (salicyclic acid) (Scotter et al. 2007), *Vanilla planifolia* (vanillin) (Kumar et al. 2010), black tea, green tea (gallic acid) (Hodgson et al. 2000; Wang et al. 2000), ellagic acid rich in pomegranate, strawberries, raspberries and walnuts (Daly et al. 2010), tannic acid rich in sorghum, millet, barley, rice, wheat, corn, soybean and other legumes (Chung et al. 1998).

Hydroxycinnamic acids are aromatic phenolic phytochemicals with a C_6-C_3 skeleton and they are hydroxy derivatives of cinnamic acid. Caffeic acid with its sources; rosemary, sage, thyme, spearmint, balm and lavender (Wang et al. 2004), cichoric acid which is a derivative of both caffeic and tartaric acid rich in the stems, leaves and roots of *Echinacea purpurea* (Thygesen et al. 2007), cinnamic acid as the main hydroxycinnamic acid in cinnamon (Ding et al. 2011), ferulic acid rich in corn bran (Zhao et al. 2005), barley (Madhujith and Shahidi 2006), wheat bran (Liyana-Pathirana and Shahidi 2006), grapefruit, orange, banana, rhubarb and berries (Mattila et al. 2006) and coumarin with its richest sources wheat, barley, oat, corn and malt (Dall'Asta et al. 2004). Capsaicin is another group of phytochemicals as the active component of chili peppers from genus Capsicum (Perva-uzunalic et al. 2004). Tyrosol is a phenethyl alcohol and a natural phenolic antioxidant with its richest source olive oil (St-Laurent-Thibault et al. 2011), hydroxytyrosol, oleocanthal and oleuropein, all of which are tyrosol esters with their richest source, olive oil (Smith et al. 2007).

Besides phenolic phytochemicals mentioned above, the second group of phytochemicals are terpenes (isoprenoids), a large and diverse class of organic compounds, produced by a variety of plants, unlike phenolic phytochemicals, they are in isoprene structure without any or a few phenolic ring in their structure. One of the most important groups of terpene with an important and anticancer effect is 'carotenes' which contribute to phytosynthesis by transmitting the light energy absorbed by the plant to chloropyll, protecting the plant tissues by helping to

absorb the energy from singlet oxygen. B-carotene is one of the most known carotenes with two retinyl groups and is broken in human mucosa of small intestine by β-carotene 15, 15-monoxygenase to retinal, a form of vitamin A. The carotenes, α-carotene and ϒ-carotene, with a single retinyl group have vitamin A activity, like β-cryptoxanthin, but less than β-carotene. Other carotenoids including lycopene have no beta-ring and thus have no vitamin A activity, but they may show antioxidant effect with different mechanisms. Chemically, carotenes are polyunsaturated hydrocarbons with hydrocarbon rings and conjugated double bonds, whose change determines the difference between alpha and beta carotene. The richest sources of beta carotene are; carrot (Berger et al. 2008), pumpkin (Azevedo-Meleiro and Rodriguez-Amaya 2007; Nestel et al. 2006), citrus fruits like tangerine and orange (Igual et al. 2013), beta carotene with its rich sources, dark green leafy vegetables (Persson et al. 2001), lycopene, a hydrocarbon carotenoid with its similar structure to β-carotene but without provitamin A activity and the strongest antioxidant with the strongest singlet oxygen-quenching capacity among other carotenes (Arab and Steck 2007), apricot, grapefruit and watermelon (Biehler et al. 2011), phytofluene, another carotenoid pigment with an orange color with its rich sources, apricot, carrot, grapefruit, orange, peach, pepper (orange or red), tomato and watermelon and phytoene, a 40 carbon intermediate in the biosynthesis of carotenoids, having a maximum UV visible absorption, ranged at 286 nm and thus another strong carotene antioxidant with its rich sources, apricot, banana, carrot, cherry, grapefruit, melon, orange, pepper (red or orange), tomato and watermelon (Biehler et al. 2011). The other group of carotenoids besides carotenes is xanthhophyll which includes the yellow leaf pigments with a similar structure to carotenes, but they contain oxygen atoms while carotenes are purely hydrocarbons with no oxygen. They are found in the leaves of green plants in the highest quantities, modulate light energy, serving a non-photochnemical quenching agent at high light levels in photosynthesis. The sources of other carotenoid, lutein, are; green leafy vegetables such as spinach or kale (Sommerburg et al. 1998; Abdel-Aal et al. 2013; Aman et al. 2005 and Azevedo and Rodriguez-Amaya 2005).

The anticancer effect of many of the mentioned phytochemicals

which are naturally exist in rich amounts in plant origin foods have been proven by many studies. Accordingly, pterostilbene in grapes and blueberries have an apoptotic and anticancer effect on DU145 human prostate, T24 and HT1376 human baldder, SK-Mel-28 melanoma (Kim et al. 2009; Kwon et al. 2012; Jayasooriga et al. 2012; Kuo et al. 2008 and Larrosa et al. 2004). Piceatannol has anticancer effect on MLL, PC3, TRAMP-C2, DU145 prostate cancer, curcumin in turmeric and mustard induce apoptosis in CTCL (T-cell lymphomas) cells, AH-130 hepatoma cells, MDA-MB-231 and MCF-7 human breast cancer cells.

TERPENES

Terpen is a class of hydrocarbons consisting of two or more isoprene (C_5H_8) units joined together. Simple terpenes are exist in essential oils and resins of plants. More complex terpenes include vitamin A, carotenoid pigments (such as lycopene), squalene and rubber. Triterpenes have got 6 isoprenes in their structure ($C_{30}H_{48}$). They may have got cyclic compounds. If they are free of cyclic (ring shape) chemical structures, they are called as 'acyclic triterpenes' which is exist in liver oil of certain species of shark (in rich amounts), but also widely distributed in nature in vegetable oils, in fungi, in human earwax. Therefore, shark liver oil may be included into the consideration of cancer nutrition and diet although more studies are needed in the field (Brittanica Academic Edition, 2011).

Triterpenes are naturally exist in vegetable oils, fruits, cereals and vegetables since they are structural components of plant cell wall. They give rigidity to the wall of the plant cell like cholesterol in the walls of animal cells. One of the greatest triterpenes discovered presently which has gained a wide consumption and application is lupeol. This triterpene is found in white cabbage, pepper, cucumber, tomato, olive oil, fig, mango, strawberry, red grapes and from herbals, American Ginseng.

Lupeol amounts as micrograms per gram in the mendioned foods are as follows; olive:3; Mango;180; Aloe vera; 280; Elm plant; 880; Japanese pear;175 and Ginseng:15.2

Today, we see a clear and strong relation between lupeol and inhibition of cancer cell proliferation. Lupeol treatment (10-100 micrograms) is shown to decrease proinflammatory cytokines such as interleukin B (Fernandez et al. 2001). Also some important studies found anticarcinogen effect of triterpenoids in various cancers that may reduce the risk 20% (Liby et al. 2007; Setzer 2003; Bradford and Awad, 2007).

The triterpenoids having got anticarcinogenic effect are namely cycloartane, lupane, friedelane, dammarane, ursane, oleanane, limonoid and cucurbitacin (Liby et al. 2007; Min et al 2001; Sporn and Suh 2000).

Triterpenes directly inhibit tumor growth, slow cell cycle progression and induce apoptosis. Especially, Lupeol from triterpenes inhibits HL-60 leukemia cells (Aratanechemuge et al 2004) while sensitizing pancreatic cancer cells to TRAIL therapy (Murtaza et al 2009). They were also claimed as inhibitory on prostate (Saleem et al. 2009) and breast cancer cells (Lambertini et al. 2005) by reexpressing estrogen receptor alpha gene in breast cancer cells (Lambertini et al. 2005).

VITAMIN E and CANCER

Vitamin E is a group of fat-soluble antioxidant nutrients consisting of tocopherols and tocotrienols. Tocopherols and tocotrienols are in different forms (alpha, beta, delta and gamma) depending upon the number and position of methyl groups on the chromanol ring as α, ß, γ. (Cardenas and Ghosh 2013). The phenolic group in the chromanol moiety quenches lipid free radicals by electron reduction which is the most important antioxidant mechanism in the protection of the cell membrane integrity (Yang et al. 2013).

The richest sources of both tocopherols and tocotrienols (tococromanols) were informed as follows; α-tocopherol content of wheat germ: 192 mg/100g and sunflower oil: 59 mg/100g, gamma tocopherol contents for camelina: 72 mg/100g, linseed: 52mg/100g and organic rapeseed oil: 51 mg/100g, total tocopherol contents for coconut fat: 4.2 mg/100 g, wheat germ oil: 268 mg/100g (Schwartz et al. 2008), alpha tocopherol content of grape seed: 25 ng/mL, gamma tocopherol content for grape seed: 43 ng/mL, gamma tocopherol content of maize:1034 mg/Kg (Şeker et al. 2012), gamma tocotrienol content of maize: 161 mg/Kg, alpha tocopherol content of rapeseed: 202 mg/Kg, gamma tocopherol content of rape seed: 490 mg/Kg, alpha tocopherol content of soybean: 100 mg/Kg, gamma tocopherol content of soybean: 1021 mg/Kg, alpha tocopherol content of maize: 282 mg/Kg, alpha tocopherol content of sunflower: 670 mg/Kg (Padley et al. 1994). Tocopherols are reported to exist most commonly in a greater ratio in plants in chloroplasts, vacuoles, nuclei, the plastids in seeds, cytoplasmic lipid bodies and leaves (Dolatabadian et al. 2008; Rautenkranz et al. 1994; Athar et al. 2009; Shigeoka et al. 1986; Kusmic et al. 1999 and White et al. 2006).

Possible mechanisms to explain the anticancer effect of the vitamin

The vitamin is the major lipid soluble antioxidant in cell membranes, a free radical scavenger and inhibits lipid peroxidation which results in the protection of cell against carcinogen induced DNA damage (Klein et al. 2003). Confirming the anticarcinogenic potential of the vitamin due to its antioxidant capacity, Shahar et al. (2008) determined a significant increased risk of breast cancer in women and greater level of malondialdehyde 4.4±1.1 mmol/g protein as an indicator of oxidative stress in women with breast cancer with lower vitamin E intakes when compared with healthy women with the higher intakes of the vitamin. Thus, the antioxidant potential of the vitamin may be one of the factors for its anticarcinogenic effect.

Multiproapoptotic signaling due to the effect of α-tocopherol from different dimensions

APO2 ligand, the cytotoxic cytoxine (the diverse group of soluble proteins, peptides and glucoproteins which act as hormonal regulators), interacts with various receptors which transmit DR4, DR5 (Death Receptors), the receptors to induce apoptosis as the new and recently described members of the tumor necrosis factor receptor family (Chaudhary et al. 1997). On the other hand, α-tocopherol triggers apoptosis due to destabilization of mitochondria, lysosomes and caspase-3 (proteins from protease-caspase family which are activated by killer T cells and directed into cells by T cells for apoptosis through signaling) (Gallaher et al. 2001). α-tocopherol maximizes the antitumor potential of APO2 ligand because the vitamin has a different antitumor effect by using a different proapoptotic signaling which results in destabilization of mitochondria, lysosomes and caspase-3 activation whereas APO2 ligand use another different proapoptotic signaling by interacting receptors that transmit DR4 and DR5. The apoptosis induced by the two mentioned mechanisms also explains the enhancing effect of the vitamin on anticarcinogen potential of APO2 ligand (Weber et al. 2002).

The inhibition on vascularization by α-tocopherol succinate

This form of α-tocopherol was reported to inhibit the expression of vascular endothelial growth factor, an angiogenic cytokine in breast cancer cells and as a result, lower vascularity in tumors (Malafa and Neitzel 2000; O'connor et al. 2000). Hence, one of the anticarcinogenic effects of the vitamin may be attributed to its contribution to the inhibition of vascularity in tumors.

Inhibition on tumor suppressors

Vitamin E inhibits tumor cell proliferation by enhancing the effect of p53, the tumor suppressor protein that is encoded by the TP53 gene, which controls another protein, p21, to control tumor cell proliferation (Nargi, Ratan and Griffin 1999). Additionally, the vitamin, like vitamin C, increases the production of TNFα (Jeng et al. 1996). TNF as the most potent inducer of apoptosis (Rath and Aqqarwal 1999) shows an important cytotoxic effect on tumor cells by inducing trimerization of specific receptors and recruitment of adapter proteins in tumor cells which result in alteration of intracellular signaling among these cells (Liu et al. 1996).

Synergism with Photodynamic Therapy (PDT) to induce apoptosis

Photodynamic Therapy, the novel treatment for cancer which targets the tumor cells to kill them by forming reactive oxygen species and using their destructive effects on the membranes of tumor cells. Vitamin E has been shown to decrease the viability of HeLa cells (the human cervical carcinoma cell line) during the treatment of tumor cells with photodynamic therapy (Al-Sherbini et al. 2009).

Protection against cancerogens in smoke of tobacco

Another reason for the anticancer potential of the vitamin may be due to the significant protection by the vitamin against the induction of DNA damage induced by tobacco specific nitrosamines, nitrosonornicotine and 4-N-methyl-N-nitrosamino-1-3-pyridyl-1-butanone, the metabolites of nicotine which are the major carcinogens in the smoke of cigarette (Weitberg and Corvese 1997).

Difference of the form as an important factor and determiner on anticancer potential of the vitamin

One of the important factors that determine the anticarcinogenic effect of the vitamin like in many other vitamin and minerals is its form. Even the small differences in structure of the vitamin's isoforms have a significant effect on its metabolism and thus in its anticarcinogenic and antioxidant potential. Confirming this, vitamin E succinate in A549 cells, lung cancer cells and gamma tocopherol via to nitrogen oxide metabolism are the two forms of the vitamin which have got higher anticarcinogenic potential (Quin et al. 2005;Christen et al. 2002). Gamma tocopherol plays an extremely important role depending against systemic inflammation caused by reactive nitrogen oxide compounds such as nitrogen dioxide and peroxynitrite, both of which are the major components of automobile exhaust and cigarette smoke which may enhance cancer and metastasis (Christen et al. 2002; Richters and Richters 1989). Another example for the difference in anticancer effect of the vitamin due to its different forms is the study of Neuzil et al. (2001) which shows the superior anticancer effect of succinyl moieties of the vitamin as compared with only alpha tocopherol form. Confirming this, alpha tocopheryl succinate could show a stronger anticancer effect in human breast cancer cell line MCF-7, lung adenocarcinoma A549 and colon cancer cell lines (DKO-1, DKO-3, DKS-5, DKS-8, DLD-1, HCT-15 and HCT-16) as compared the form, alpha tocopherol by inactivating protein kinase C (PKC), a group of enzymes that linked to carcinogenesis (Koivunen et al. 2006).

Conflicted studies that claim the carcinogenic effect of vitamin E and the possible resasons: The form and the combined use matters

The vitamin's family consists of eight molecules having a chroman ring with an alcoholic hydroxyl group and a 12-carbon aliphatic side chain containing two methyl groups in the middle and two more methyl groups at the end of the aliphatic side. The aliphatic sides of four members in the family of the vitamin is saturated which are called tocopherols whereas the other four members (tocotrienols) contain three double-bonds all of which adjoin a methyl group in their aliphatic sides. The four tocopherols and the four tocotrienols have an alpha, beta, gamma and delta form based on the number and position of the methyl groups on the chromanol ring (the chroman ring with an alcoholic hydroxyl group). The alpha form has three methyl groups, the beta and gamma forms have two methyl groups each and the delta has one methyl group. The main anticarcinogenic effect of vitamin E is due to the antioxidant effect of these forms in different chemical structures which protects DNA from the damage of free oxygen radicals. Followed by the absorption of the vitamin and its reach into cell membrane by the means of blood circulation, the polar chroman ring tends to stay near the edges of the membrane whereas the hydrophobic core penetrates deep into membrane. When the phospholipid tail becomes peroxidized by a free radical by giving H from its tail, the tail becomes more polar and migrates to the surface where it meets the tocopherol chroman ring to be neutralized, forming a 'tocopheroxyl' radical. The tocopheroxyl radicals can be reduced to tocopherol directly by vitamin C and then by glutathione or lipoic acid which are in turn reduced by NADH or NADPH. This detail points out the necessity of the combined use of tocopherol and vitamin C to be able to neutralize the oxidant radical of tocopherol. Otherwise, the oxidant radical 'tocopheroxyl' which forms during the neutralization of other free oxygen radicals by tocopherol may initiate another chain reaction of oxidation. A new question appears

at this stage. Could it be correct to define and classify the antioxidants as rather oxidants while some of the antioxidants like in this example can inhibit the pro-oxidation with the support of some other antioxidants?. Another reason for the necessity of the combined use of vitamin C and vitamin E is that both vitamins can compensate for decline in glutathione which is one of the important anticancerogens, associated with aging, many times as both in a significant synergistic chemoprevention of cancer with beta caroten and glutathione (Lenton et al. 2003; Shklar et al. 1993). But the most important reason for the necessity of the combined use of both vitamins with the current knowledge seems that ascorbate (a vitamin C form) and alpha-tocopherol are water soluble and fat soluble antioxidants which interact and work synergically to form a non enzymatic antioxidant system in the aqueous phase (cytosol) and the lipid phase (plasma membrane and membrane of cell organelles). Thus, the two most important oxidant radicals, OH-(hydroxyl) and O_2- (superoxide), are neutralized by ascorbate in aqueous phase, while they are neutralized by alpha tocopherol in lipid phase (Sharma et al. 2013). Nevertheless, many studies about cancer nutrition seem to neglect to study the anticancer potential of the combined use of the vitamin with other vitamins and minerals. Some of these studies even claim the vitamin as a cancer promoter rather than anticancer. In addition to the failure of the alone use of the vitamin, another reason for these claims may be the form. Some studies that claim the carcinogenic effect of the vitamin shows the reason as the higher rate of free radical production of alpha form. Additioanlly, gamma tocopherol with its weaker antioxidant capacity than alpha tocopherol was shown to inhibit cell proliferation as well as DNA synthesis in various cancers decreasing levels of cyclin D1 and cuclin E, the proteins that are involved in regulating cell cycle progression and proliferation (Gysin, Azzi and Visarius 2002). The weaker antioxidant potential of gamma form may have killed cancer cells while causing less harm to healthy cells with its weaker antioxidant potential.

Nitric oxide (NO) is an important signaling molecule which is produced in many tissues including the blood vessel endothelium and the brain. The molecule regulates many physiological processes which involve vasodilation, neurotransmission and modulation of

the hair cycle while inhibiting vascular smooth, muscle contraction, platelet aggregation and leukocyte adhesion to the endothelium. The most important pathologic effect of nitric oxide is one of its most toxic radicals and cancerogens, peroxynitrite, produced by its reaction with superoxide (O_2-) onion. In contrast to alpha-tocopherol, gamma tocopherol was found as having a stronger ability to scavenge nitrogen dioxide (that arises via the oxidation of nitric oxide by oxygen) without forming toxic and cancerogen nitrogen products like peroxynitrite (Cooney et al. 1993). Gamma form was also found as an essential to remove peroxynitrite-derived toxic products (Christen et al. 1997).

Confirming the difference in anticancer potential due to the form, tocopherols and tocotrienols were shown to have different potencies in suppressing tumor cell growth and inducing apoptosis in neoplastic mammary epithelial cells (McIntyre et al. 2000), while the administrations of alpha and gamma tocotrienol but not alpha tocopherol, were found to suppress the growth of human breast and colorectal cancer cells (Nesaretnam et al. 1995; Eitsuka et al. 2006).

The study of Helzlsouer et al. (2000) seems one of the cornerstones which clearly present the importance of the form and its association with the anticarcinogenic potential. The findings of this huge study with 10456 male, 117 prostate cancers and 233 controls indicated that the risk declined with increasing alpha tocopherol concentration but gamma form had a fivefold reduction in the risk while the significant protective associations for high levels of selenium and alpha tocopherol were observed only when gamma tocopherol concentrations were high. Confirming these findings, Jiang et al. (2004) and Lu et al. (2010) inhibited H1299 human lung cancer and LNCaP prostate cancer cells with gamma form while there was no any effect of alpha form on these cancer cell lines. Jiang et al. (2001), Dietrich et al. (2006) and Gysin et al. (2002) confirmed similarly the superior anticarcinogenic potential and antitumor activity of gamma form. One of the reasons for the superior anticancerogenic effect of gamma form may be its greater inhibition on COX-2 (cyclooxygenase 2; the enzyme that is responsible for the inflammatory hormones such as prostaglandins, prostacyclins and thromboxanes) (Jiang et al. 2000) and its greater capability to

scavenge reactive nitrogen species which can damage proteins and DNA and hence cause cancer.

Two forms of vitamin E, gamma and alpha, were shown to be inhibitory on prostate cancer by inhibiting the activation of an enzyme called Akt which is essential for cancer cell survival. Confirming the importance of 'form' factor in anticancer potential, the inhibition was detected superior in gamma form. Both forms, especially gamma, were not only claimed to inhibit Akt but also activated another protein PHLPP1, a tumor suppressor in the fat-rich cell membrane where the vitamin was absorbed. The reason for the superior anticancer effect of gamma form might be due to its chemical shape which might allow it to attach to the enzyme, Akt, in the most precise way to shut it off. The same researchers also made manipulation on the chemical structure of gamma form by lopping off about 60% of its side chain so that the head group was more accessible to Akt and PHLPP1. As a result, they could observe the greater anticancer effect on prostate cancer cells injected with the manuplated gamma form in animals (Huang et al. 2013). Although the study is currently a non completed study which waits for patent and its application on human subjects, its findings are vitally important, indicating to the crucial factors which should be taken into consideration in the further studies related to nutrient and cancer relations. These crucial factors are; 1. The form of the vitamin may always affect its anticarcinogenic potential and 2. Any manuplation on the chemical structure of vitamin may significantly affect its anticarcinogenic potential.

The knowledge about tocotrienols became limited since they are less abundant than alpha and gamma tocopherol in blood circulation and in solid tissues. Lately, the recent findings significantly contributed to highlight their role in cancer. The hypomethylated chroman ring has been reported to be responsible of signaling effects that differentiates them from other forms (Galli and Azzi 2010): Specifically, the combination of the hypomethylated chroman ring with the isoprenyl moiety is that of producing a response of bioavalibility and transformation, resulting in their superior anticancer effect. Another reason for the greater anticancer potential may be the vitamin E binding protein that this protein binds the fully methylated and saturated form, alpha tocopherol, with 10-fold

higher affinity than tocotrienols, causing a less and limited anticancer effect of alpha tocopherol which causes a decrease in its bioavalibility (Hosomi et al. 1997). The other important contributer for the superior anticancerogenic potential of tocotrienols may be its low affinity to the binding proteins, besides vitamin E binding protein, like α-TTP(α-tocopherol transfer protein, the protein which binds alpha tocopherol, enhances its transfer between separate membranes and stimulates its release from cells) (Atkinson et al. 2008), intracellular receptors like Erβ (tumor promoting estrogen receptor) (Camitato et al. 2000) and orphan receptors like SXR (streoid and xenobiotic receptor that promotes cancer growth by regulating cell proliferation)(Zhou et al. 2004). One of the strongest contributors to the anticancerogen potential of tocotrienols is that they may co-localize and interact with polyunsaturated fatty acids and cholesterol molecules in the cell membrane to influence the composition and function of the membrane which may result in the control of cell signaling and redox responses through NADPH-oxidase (nicotinamide adenine dinucleotide phosphate-oxidase, e membrane-bound enzyme complex that generates superoxide by transfering electrons from NADPH) and PKC (Protein kinase C, the enzyme that is involved in controlling the function of other proteins through phosphorylation (Galli 2007; Eitsuka et al. 2006; Theriault et al. 2002).

Telomerase, an enzyme in ribonucleoprotein structure, that adds DNA sequence repeats ('TTAGGG') to the 3' end of DNA strands in the telomere (repetitive nucleotide sequences at each end of a chromatid which protects the end of the chromosome from deterioration) regions. Shortening of the telomeric DNA at chromosome ends is postulated to limit the lifespan of human cells. In contrast, activation of the enzyme that synthesizes telomeric DNA is proposed to be an essential step in cancer cell immortalization and cancer progression (Meyerson 2000). Telomerase seems to be activated in 80-90 % of human carcinomas (colorectal carcinoma cells from luminal washings, lung carcinoma cells from bronchial washings, bladder carcinoma cells from urine or bladder washings, breast carcinoma or thyroid cancer cells from needle aspirations, squamous carcinoma cells from oral rinses) (Chen and Chen 2011). On the other hand, the length and activity of telomerase were

shown to decrease by tocotrienol (Makpol et al. 2011), which may be another contributer to their superior anticancer potential.

Kappa tocotrienol was shown to inhibit the secreation of hypoxia-induced VEGF, vascular endothelial growth factor, the signal protein produced by cells that stimulates vasculogenesis and angiogenesis as a part of the system that restores the oxygen supply to tissues when blood circulation is inadequate as in human colorectal adenocarcinoma (DLD-1) and human hepatoma cell lines (HepG2). Also, the same tocotrienols reduce the expression of HIF-1α protein, the protein that binds to specific DNA sequences, controlling the flow of genetic information from DNA to messenger RNA and as a result, responds to changes in available oxygen in cell, specifically to decrease in oxygen, hypoxia. Finally, kappa tocotrienols exhibited a potential to suppress the expression of hypoxia-induced COX-2 (Cyclooxygenase 2), the enzyme that is responsible for the production of inflammatory prostaglandins which cause inflammation and pain and IL-8 (Interleukin 8), signaling protein produced by macrophages which induces phagocytosis and chemotaxis, causing neutrophils to migrate to the side of infection, in the same cancer cell lines (Shibata et al. 2008). Briefly, the superior anticancerogenic effect of tocotrienols may be explained as due to their inhibitory effect on IL-8, COX-2 and VEGF, all of which may cause cancer by increasing the rate of angiogenesis, vasculogenesis, hypoxia and inflammation.

Another explanation for the superior anticarcinogenic effect of tocotrienols may be due to the relation between tocotrienols and tocotrienol responsive genes since the transcript of tocotrienol responsive genes involves detoxification and antioxidant elements such as quinone reductase and heme-oxygenase (Das et al. 2008; Hsieh and Wu, 2008).

Tyrosine kinase, the enzyme responsible for catalyzing the phosphorylation of tyrosine residues in proteins, is involved in the cell-cycle control and properties of transcription factors (Radha et al. 1996). The intracellular tyrosine kinase domain allows the interaction and phosphorylation of intracellular substrates involved with the regulation of signaling pathways (Normanno et al. 203; Schlessinger, 2000). Υ-tocotrienol causes a large relative reduction in total levels of Met, a receptor tyrosine kinase that plays a role in regulating numerous

biological functions including mitogenesis and metastasis. Υ-tocotrienol as combined with a tyrosine kinase (Met) inhibitor, SUII274, was found to inhibit MCF-7 and MDA-MB-231 breast cancer cells (Ayoub et al. 2013).

Peroxisome proliferator activated receptor Υ (PPARY) is a group of nuclear receptor proteins that function as transcription factors, regulating the expression of gens and thus cellular differentiation, development, metabolism and tumorigenesis. The agonists of PPARY such as rosiglitazone and troglitazone when combined with Υ-tocotrienol administration were found to inhibit MCF-7 and MDA-MB-231 breast cancer proliferation (Malaviya and Sylvester 2013).

Phospholipase A2 is the enzyme that releases fatty acids from the second carbon group of glycerol. These fatty acids released by the enzyme are also the substrates for intracellular biochemical pathways that generate lipid mediators such as eicosanoids and platelet activating factors which in turn regulate cell proliferation and vascularization. Tumor growth in prostate cancer is dependent on the enzyme (Scott et al. 2010) while the knockdown of secretory phospholipase A2 enzyme reduces lung cancer growth (Yu et al. 2012). The effect of tocotrienol at this stage which contributes to its superior anticancerogenic effect is its inhibition on the enzyme (Khanna et al. 2010; Patel et al. 2011) which limits the energy production and vascularization in tumors.

12 lypoxygenase, the iron containing enzyme that catalyses the dioxygenation of polyunsaturated fatty acids (fatty acid+O_2=fatty acid hydroperoxide), constitutes a pathway for arachidonic acid whose release from membrane phospholipids is essential for tumour cell proliferation (Honn et al. 1994). The enzyme utilizes arachidonic acid to synthesize 12 (S)-hydroperoxyeicosatetraenoic acid. 12 (S)-hydroperoxyeicosatetraenoic acid is converted to the end product, 12 (S)-hydroxyeicosatetraenoic acid, an eicosanoid which promotes tumorigenesis and metastasis. One of the findings that clearly show this tumor promoting effect is the 3-fold increase in VEGF level by the overexpression of the enzyme in prostate cancer cells, PC-3 (Nie et al. 2006). Confirming this, inhibition of the enzyme activity was shown to induce apoptosis in human gastric cancer cells (AGS and MKN-28) (Wong et al. 2001) while its increased expression was observed in breast

cancer cells, MCF-7 and COH-BR1 (Natarajan et al. 1997). On the other hand, tocotrienol modulates and inhibits 12-lipoxygenase (Khanna et al. 2003; Patel et al. 2011 and Khanna et al. 2013) that this effect may be another contributer for the superior anticancer potential of tocotrienols when compared with the other forms of vitamin E.

Nuclear factor kβ (NF kappa β: Nuclear Factor kappa-light-chain-enhancer of activated β cells) is the protein that controls the transcription of DNA and is involved in cellular responses to stimuli such as stress, cytokines, free radicals while its incorrect regulation has been linked to cancer (Karin 2006; Bours et al. 2000; Aggarwal, 2004; Fujioka et al 2003). Nuclear factor kβ may be a strong parameter to explain the reason for the superior anticancer effect of tocotrienol than tocopherol since gamma-tocotrienol can completely abolish tumor necrosis factor alpha (TNF) induced kappaβ activation whereas similar dose of gamma-tocopherol has no effect. Gamma tocotrienol abolishes NF-kappaβ activation induced by phorbol myristate acetate, okadaic acid, lipopolysaccharide, cigarette smoke, interleukin-1beta and epidermal growth factor (Ahn et al. 2007). Similar anticancer effect were also informed by inhibiting NF-kβ on various cancers including neoplastic mammary epithelial cells, pancreatic cancer cells (BxPC-3, MIAPaCa-2, PANC-1, HPDE6C7, HPDE6-7-KRas), breast cancer cells (MCF-7), human oral cancer cells (B88) (Shah and Sylvester et al. 2013; Kani et al. 2013 and Husain et al. 2011; Loganathan et al. 2013).

Tocotrienols also suppresses tumorigencity through inactivation of the PI3/AKT/β-catenin (the proteins linked to cell growth, differentiation, adhesion and gene transcription) pathway (Linget al. 2012).

Epidermial growth factor receptor 2 (HER 2) is a proto-oncogene (means a normal gene which can become an oncogene, a normal gene, but may gain a cancerogen character due to mutation or increased expression) in breast cancer. The gene functions through mitogen-activated protein kinase (MAPK: serine/threonine-specific protein kinases which utilizes cellular responses to stimuli such as mitogen, osmotic stress, heat, shock and proinflammatory cytokines), phosphoinositide 3-kinase (PI3K/ Akt), phospholipase C (PCL) (the enzyme that cleaves phospholipids, creating signal transduction pathways), Signal transducer and Activator of Transcription (STAT) (the protein that regulates cell growth, survival

and differentiation through signal creation). Thus, amplification or over-expression of HER-2 and PI3K/Akt may result in uncontrolled cell growth, cancer (Sheppard et al. 2012; Baselga, 2011). On the other hand, an inhibition on the PI3K/Akt signaling pathway results in the tumor cell growth arrest and apoptosis like in the case of tocotrienols. Tocotrienols were proven and claimed as the novel PI3K/Akt and HER2 inhibitors causing an antitumor effect (Sylvester and Ayoub 2013; Chakraborty et al. 2011; Nesaretnam and Meganathan 2011; Aggarwal et al. 2010; Bachawal et al. 2010; Shin-Kang et al. 2011).

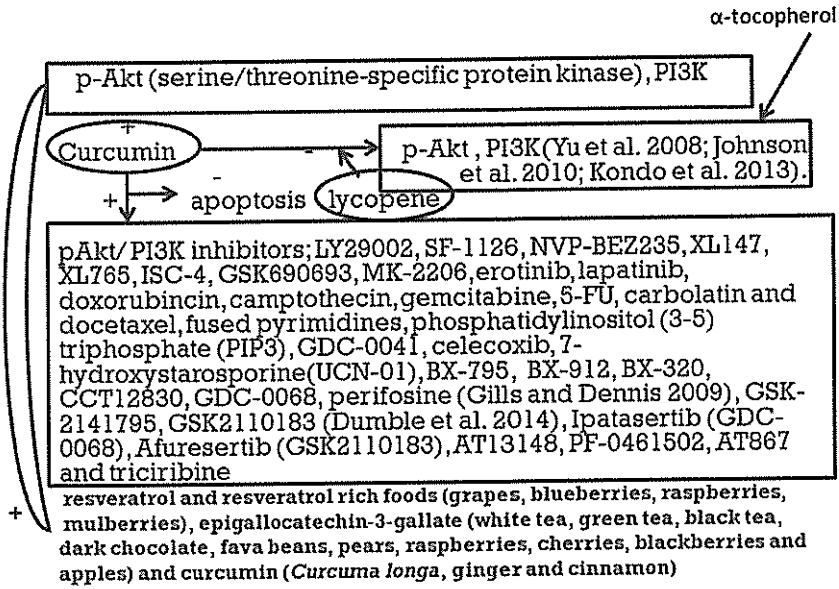


FIGURE 4

PPARG, Peroxisome proliferator-activated receptor gamma, a nuclear receptor which regulates fatty acid storage and glucose metabolism, stimulates lipid uptake and adipogenesis by fat cells. The inhibition of the receptor may result in hyperlipidemia which may increase the rate of free radicals in cancer potential. Y-tocotrienol as combined with PPARG agonists, rosiglitazone or troglitazone, was determined to cause an antitumor effect by inhibiting PPARG in breast cancer cells, MCF-7 and MDA-MB-231 (Malaviya and Sylvester 2013).

The strong relation between cancer and red meat consumption was previously referred above. Like the relationship between all processed food products and cancer, the increase in processed red meat product consumption significantly increases the risk of cancer formation. One of the reasons of the close relation between processed red meat and cancer is the high amount of cholesterol, bad cholesterol and saturated fat in these products. As clearly mentioned above, the excess of cholesterol and bad cholesterol is not only a risk factor for atherosclerosis (calcification), hypertension and other cardiovascular diseases and disorders, it may be a reason for the progress of cancer. Because, excess of these substances can be converted into carcinogenes and may enter into cell, change the genom of the cell, which may result in cancer. For these reasons, red meat consumption should not be in high amounts while it should be as in low amounts as possible. Separation of the fat manually before cooking, cooking in simmering water for one or two minutes until the fat globules appear on the surface and elimination of this surface method and then using the meat bulk in cooking may be beneficial practical application in reducing the total fat. Regular blood check as two times a year within 6 months intervals should be a must to be able to monitor the total fat in body. The total serum trigiliserid amount should never exceed 220 mg/mL while the total cholesterol should be lower than 200 mg/mL and the good cholesterol (low density lipoprotein) should be 60 mg/mL or more. Especially, the close relation between good cholesterol and cancer should never be neglected. In case of good cholesterol consideration, always hypertension and similar cardiovascular diseases and disorders are taken into evaluation. But, there is also a great link between this compound and cancer. Because, good cholesterol takes the cholesterol from the wall of blood vessel and gives it back into the blood stream as in free form. The free cholesterol particules can be eliminated by the means of kidneys and urin after the action of good cholesterol and can not find opportunity to be converted into carcinogenic substances. Opposite, bad cholesterol (low density lipoprotein) binds the free cholesterol from blood and binds it on the surface of blood vessels. The more fat accumulation on the surface of blood vessel is an opportunity for the more fat globul convertion into carcinogen. Higher fat, saturated fat, trigiliserid and bad cholesterol amounts in blood stream are always

predisposed factors which increase not only cardiovascular diseases and disorders but also various cancers.

The strongest adverse effect of the high fat, saturated fat and cholesterol concentrations in blood appears in kidneys. The filtering vessels which are very tiny and small in diameter size can easily be calcified by high cholesterol, bad cholesterol, trigliserid and saturated fat and kidneys become insufficient to filter these toxic compounds from blood because of the kidney's calcified filterin vessels. The result is the accumulation of some toxic substances which are formed by the decomposition of proteins in blood such as uric acid, kreatin, histidin, histamin. These substances in addition to cholesterol, saturated fat, bad cholesterol, excess of salt and sugar alltogether may accumulate around the cell membrances. They may rupture the cell wall when they are in huge concentrations by making a mechanical pressure against the wall, can enter into the cell and change the genom of the cell which may also cause cancer. Briefly, not only life but also kidneys should be protected from excess of saturated fat, cholesterol and bad cholesterol, sugar and salt which are all exist in plenty amounts in processed red meat products.

It should always be taken into consideration in every period of life that, saturated and unsaturated fat, trigliserid, salt, sugar, cholesterol and bad cholesterol are not the only harmful substances that increase the risk of cancer. But also, all these mentioned substances are the initial causes for aging. Their accumulation around the cells can wound or rupture the cell walls and thus kill the cells or wound them by making mechanical pressure against the walls of the cells. The increase in wounded cells or death cells because of these harmful substances or their toxic radicals is the main reason for organ and tissue aging and deficiencies. The organ and tissue aging and deficiency is another strong predisposed factor in increasing the risk of cancer. Vitamin E shows a very similar chemical structure to fatty acids and they are oxidized by using this similarity in chemical structure instead of fats without yielding free toxic peroxy radical compounds. Therefore, they help for the decrease of free toxic peoxy radical concentration in blood which may then be converted into carcinogens. The *concentration* of free toxic peroxy radicals in blood may remain very high for long periods of life without vitamin E since

more fat can be oxidized and yield more free toxic peroxy radicals without the vitamin and this may naturally increase the risk of cancer.

One of the most important beneficial effect of the vitamin is the protection made by the vitamin against nitrit and nitrat, the food additives which are commonly used in plenty amounts in many processed red meat products such as salami, sausage, ham and dried meat soups. These food additives are added into the processed meat products during production because they kill harmful bacteria which cause food posioning and infections and hence extend the shelf life of the end product while protecting public health. One of the most harmful bacteria which is very resist to very high temperatures since it produces its resist form, spore, under heavy conditions such as high temperature and humidity, is *Clostridium botulinum*. The bacteria can contaminate consumer by the consumption of canned products. Since the bacteria cause fermentation and produce gas in packaging material, it may be helpful to pay attention whether a bombage is exist in packaging material during Marketing. On the other hand, nitrite and nitrate kill *Clostridium botulinum* while killing many other bacteria species. Briefly, the extension of shelf life and the protection of consumer against harmful bacteria species are the main reasons for the addition of these food additives. Unfortunately, the long term consumption of nitrite and nitrate added processed meat products may trigger the cancers in stomach and intestine origin. Nitrite and nitrate as closely integrated into meat products become free in the cavity of stomach and combine with the decomposed end products of meat proteins which are called as 'amin' and produce 'nitrosoamin'. These compounds are one of the initial and most common causes of stomach, intestine, colon and rectum cancers. All of us may have consumed less or high amount of processed red meat products or some of us might have consumed. On the other hand, the consumption of food products rich in vitamin E can reduce the risk of such cancers in stomach and intestine because of nitrat and nitrit (Packer 1991; Duthie et al 1989).

Vitamin E food sources

Vitamin E food sources	Vitamin E content (alpha-tocopherol) (mg/ 100 g food)
Oil, vegetable, sunflower, linoleic (approx. 65%)	41.10
Oil, vegetable safflower, salad or cooking, oleic, over 70% (primary safflower oil of commerce)	34.12
Seeds, sunflower seed kernels, dry roasted, with salt added	26.10
Seeds, sunflower seed kernels, dry roasted, with salt added	26.09
Nuts, almonds	25.86
Nuts, mixed nuts, dry roasted, with peanuts, with salt added	10.93
Nuts, pine nuts, dried	9.35
Nuts, pine nuts, dried	9.35
Snacks, potato chips, plain, unsalted	9.10
Peanuts, all types, dry-roasted, with salt	7.80
Tomato products, canned, paste, without salt added	4.30
Spinach, frozen, chopped or leaf, cooked, boiled, drained, without salt	3.54
Dandelion greens, cooked, boiled, drained, without salt	3.40
Turnip greens, frozen, cooked, boiled, drained	2.66
Pie crust, standard-type, frozen, ready-to-bake, baked	2.63
Turnip greens, frozen, cooked, boiled, drained without salt	2.66
Pie crust, standard-type, frozen, ready-to-bake, baked	2.63
Pie crust, cookie-type, prepared from recipe, graham cracker, baked	2.32

Turnip greens, frozen, cooked, boiled, drained without salt, without salt	2.66
Pie crust, standard-type, frozen, ready-to-bake, baked	2.63
Pie crust, cookie-type, prepared from recipe, graham cracker, baked	2.32
Tomato products, canned, sauce	2.08
Spinach, cooked, boiled, drained, without salt	2.08
Sauce, pasta, spaghetti/marinara, ready-to-serve	2.04
Tomato products, canned, puree, without salt added	1.97
Spinach, canned, drained solids	1.94
Turnip greens, cooked, boiled, drained, without salt	1.88
Crustaceans, crab, blue, canned	1.84
Beet greens, cooked, boiled, drained, without salt	1.81
Fast foods, french toast sticks	1.65
Peppers, sweet, red, cooked, boiled, drained, without salt	1.65
Fast Foods, biscuit, with egg and sausage	1.58
Peppers, sweet, red, raw	1.58
Fish, rockfish, Pacific, mixed species, cooked, dry heat	1.56
Broccoli, cooked, boiled, drained, without salt	1.45
Soy milk, fluid	1.35
Broccoli, frozen, chopped, cooked, boiled, drained, without salt	1.32
Carrot juice, canned	1.16
Sweet potato, canned, syrup pack, drained solids	1.15
Mangos, raw	1.12
Pumpkin, canned, without salt	1.06
Sweet potato, canned, vacuum pack	1.00
Soup, tomato, canned, prepared with equal volume water, commercial	0.95
Papayas, raw	0.73

USDA National Nutrient Database for Standard Reference, Release 18. Wagner, K.H., Kamal-Eldin, A., and Elmadfa, I. 2004.

Gamma-Tocopherol- an Underestimated Vitamin. Ann. Nutr. Metab. 48: 169-188.

Alpha tocopherol, 'alpha tocopherol and alpha lipoic acid' combination and gamma tocopherylquinone were found to increase the upregulation of caspase-3 activity (Miyoshi et al. 2005; Salerno et al. 2007; Calviello et al. 2005; Uemura et al. 2002; Marsh et al. 2005). Hence, costunolide, cisplatin, mitomycin c, garcinol, brefeldin A, valinomycin, piceatannol, kinetin riboside, lipase inhibitor, THL, imiquimod, SC560, romidepsin, ovabain, digoxin, proscillaridin A, borrelidin, sanguinarine, bortezomib, MT-21, ionidamine, K858, saikosaponin A, CIL-102 and prodigiosin, the anti-cancer agents and drugs that induce caspase activity and as a result, the release of cytochrome c, may have stronger anti-cancer potential if they are administered as combined with alpha-tocopherol or Y-tocopherylquinone (but not other tocopherols!) or the combination of alpha tocopherol and alpha lipoic acid, creating a synergy to induce caspase activity and thus inducing cytochrome c release and ROS influx. On the other hand, alpha tocopherol induces VEGF (the Vascular Endothelial Growth Factor) which has an important role as a significant contributer to angiogenesis(Zingg et al. 2015), by up-regulating the expression of PI3KY (phosphoinositide 3-kinase Y), the gene which is involved in cell growth, proliferation, differentiation, motility and survival, functioning downstream of proinflammatory G protein (heterotrimeric guanine nucleotide-binding protein-coupled receptors in neutrophils) (Deladeriere et al. 2015). Because of the mentioned inducing effect of alpha-tocopherol on VEGF, the VEGF inhibitors; sunitinib, sorafenib, bortezomib, bortezomib and MP0250 combination, MG132, MG262, KF58333, 17-AAG, geldanamycin, SNX-2112, honokiol, thapsigargin, bafilomycin A1, budesonide, brefeldin A, monensin, ritonavir, bevacizumab, ranibizumab, fulvestrant and vandetanib combination, tamoxifen, clomiphene, nafoxidine, [ICI82,780], metformin, paclitaxel, tunicamycin and PTK787/ZK222584 (vatalanib), may be contraindicated if they are administered with alpha-tocopherol or the vitamimn E richest sources like; sunflower oil, camelina, linseed, coconut, wheat germ, grape seed, maize, rape seed and soybean.

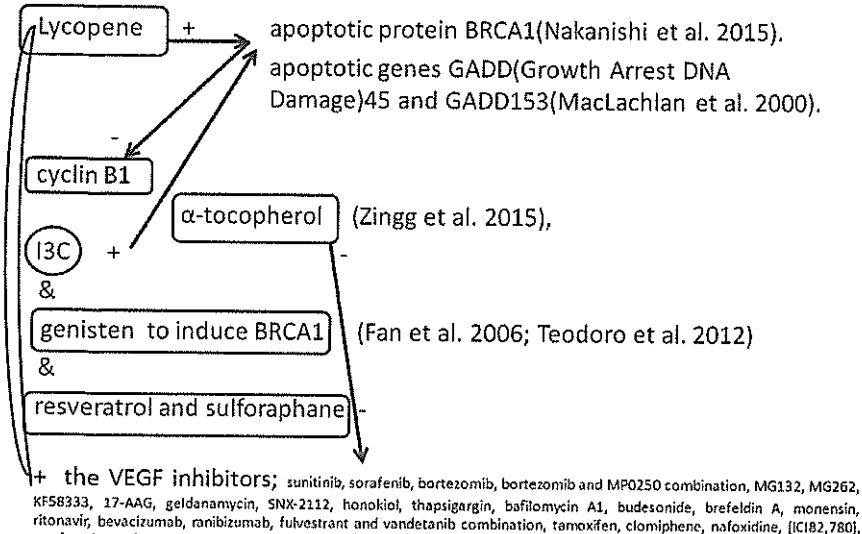


FIGURE 5

Alpha-Tocopherol succinate's one important anti-cancer effect is due to its inhibitory effect on the anti-apoptotic proteins; Bcl-2 and Bcl-xL, the proteins which prevents the release of cytochrome c while inhibiting caspase activity (Shiau et al. 2006). Therefore, the combined administration of alpha-tocopherol or a tocopherol rich consumption, e.g. sunflower oil, camelina, linseed, coconut, wheat germ, grape seed, maize, rape seed, soy and soy products, may enhance the anti-cancer potential of the Bcl-2 inhibitors; HA14-1, AT-101, obatoclax, ABT-263, ABT-737, sunitinib, sorafenib, thapsigargin, bortezomib, 17-AAG, vorinostat, honokiol, metformin, tetrandrine, tamoxifen, geldanamycin, radicicol and raloxifen.

Currently, the only study which belongs to Krishnan et al. (2010) about the effect of the vitamin on the Hedgehog signaling (Hh), the signaling which transmits information to embryonic cells for the cell development and survival, is crucial, since it claims that alpha tocopherol may trigger the signaling. The mentioned adverse effect of the vitamin against cancer prevention and treatments may indicate a possible risk of contraindication if alpha-tocopherol or vitamin E rich foods

(in rich amounts) are administered as combined with the Hedgehog (Hh) inhibitors; SANT1-SANT4, CUR-61414, HhAntag-691, GDC-0449, saridegib, phthaladines, mukul, guggulsterone, itraconazole, NVP-LDE225, TAK-441, XL-139, HTS piperidines, MRT-92, MRT-83, PF-04449913, N-acylethanolamides, endocannabionids, IPI926, BMS-833923, LEQ506, GANT61, ribotnikinin, HPI1-4, 2-acylglycerols and 2-alkylglycerol. Like alpha tocopherol, vitamin C and vitamin C rich foods, e.g. banana, broccoli(raw), cabbage(raw), grapefruit(raw), spinach(raw), tomato(raw), lettuce(raw), orange, lemon and other citrus fruits and green leafy vegetables in rich amounts, should be avoided because of their Hh inducing effects, during the anti-cancer treatments by Hh inhibitors. Unlike vitamin E and C, quercetin rich foods, e.g. caper, onion, cocoa, berries, tea, asparagus, and quercetin tablets, may be beneficial during the treatments which administer the Hh inhibitors, since quercetin may create a synergy with the mentioned Hh inhibitors, inhibiting bthe signaling.

Gamma and alpha-tocopherol succinate inhibit COX-2, the enzyme which is responsible for the production of the inflammatory cytokines (Jiang et al. 2000; O'leary et al. 2004; Egger et al. 2003; Lee et al. 2006). So, the COX-2 inhibitors in anti-cancer treatments; sunitinib, celecoxib, magnolol, honokiol, eugenol, rofecoxib, nafroxen, dexamethasone, hydrocortisone, beclamethasone diproprionate, may show greater anti-cancer potential when combined with vitamin E supplementation and/or vitamin E rich food consumption, creating a synergy via the inhibition of Cox-2.

Actinomycin D, apicidin, gossypol, AT-101, BAM7, C75, cerulenin, paclitaxel, bufalin, CHM1, curcumin, cyclophosphamide, gambogic acid, kaempferol, mitomycin-c, oxaliplatin, 2-methoxyestradiol, 2-indolinones, piperlongumine, apigenin, beta-carotene, genistein, diallyl sulfide, lycopene, I3C, arginine and sulforaphane, the anti-cancer agents and bio-active compounds that induce the pro-apoptotic protein Bax, may be more effective in cancer treatments if their administrations are combined with vitamin E supplementation or/and vitamin E rich food consumption since alpha-tocopherol succinate, like the mentioned ones, induce up-regulation of Bax (Khanduja et al. 2008). A complex diet of quercetin, apigenin, beta-carotene, genistein, diallyl sulfide, lycopene,

I3C, arginine, sulforaphane rich foods/supplements as combined with vitamin E rich foods and/or tocopherol-mix supplements, may be advised during the anti-cancer treatments using the mentioned Bax inducers to increase the level of Bax up-regulation (Khanduja et al. 2008).A complex diet of quercetin, apigenin, beta-carotene, genistein, diallyl sulfide, lycopene, I3C, arginine, sulforaphane rich foods/supplements as combined with vitamin E rich foods and/or tocopherol-mix supplements, may be adviced during the anti-cancer treatments using the mentioned Bax inducers to increase the level of Bax up-regulation.

Alpha-tocopherol may be beneficial in anti-cancer treatments which use IL-inhibitors; tocilizumab, sunitinib, sorafenib, metformin, radicicol, 17-AAG, monensin, brefeldin A, raloxifene, bortezomib, siltuximab, honokiol and curcumin since the pro-vitamin inhibits IL-6, the cytokine which induces inflammation, angiogenesis and tumor growth (Godbout et al. 2004). For this reason, the foods/plants rich in both curcumin (e.g. *Curcuma langa*, cinnamon and cinnamon containing foods) and vitamin E (e.g. Camelina, linseed, coconut, sunflower oil, wheat germ, grape seed, maize, rape seed, soybean and soy products), may be the skeleton for the diet to follow during anti-cancer treatments which target IL-6 inhibition.

The inhibition of iNOS, the enzyme which produces NO, modulating angiogenesis and metastasis, by alpha tocopherol (Chen et al. 2002) may enhance the anti-cancer potentials of the treatments which use iNOS inhibitors namely; L-arginine, L-canavanine, L-NAMA (NG-nitro-L-arginine methyl ester hydrochloride), L-NNA (L-NG-nitroarginine), N6, NG-dimethyl-L-arginine, L-NIL [L-N6-(1-iminoethyl) lysine dihydrochloride], NILT (N6-iminoethyl-lysine tetrazoleamide), L-NIO [N(5)-(-(-iminoethyl)-L-ornithine], vinyl-L-NIO, AMT(2-amino-5,6-dihydro-6-methyl-4H-1,3-thiazine), L-thiocitrulline, S-methyl-L-thiocitrulline, N-propyl-L-arginine, 1400W, A-guanidiglutaric acid, S-(2-aminoethyl)isothiourea, EIT hydrobromide, Mercaptoethylguanidine, S-ethylisothiourea, S-methylisothiourea, 1,3-PBIT) [1,3-S,S-1,4-phenylenebis (1,2-ethanediyl)bis-isothiourea], 1,4-PBIT, Aminoguanidine, 2-imino-4-methylpiperidine, TRIM (1-[2-trifluoromethylphenyl] imidazole, 7-nitroindazole, 3-bromo-7-nitroindazole and BYK-191023

dihydrochloride (2-[2-(4-Methoxy-2-pyridinyl)ethyl]-1H-imidazol [4,5-b] pyridine dihydrochloride).

The inhibition of GRP78, the central regulator of endoplasmic reticulum (ER) and the chaperon which controls ER with its protein folding capacity, is one of the significant anti-cancer potentials of alpha-tocopherol succinate when it is at 5-20 μg/mL concentrations (Huang et al. 2010). Therefore, the vitamin E may enhance the anti-cancer potential of the anti-cancer drugs; sunitinib, sorafenib, SCH727965, metformin and bortezomib combination, tunicamycin, radicicol, KUSs, versipeolstatin, pyrivinium pamoate, tanespimycin and 17-AAG, the drugs all of which target cancer cells by inhibiting the chaperon and β-catenin signaling, like the vitamin.

Alpha-Tocopherol succinate induces the proapoptotic proteins; Foxo1 and Foxo3a (Valis et al. 2011). Therefore, the Foxo3 inducers; metformin, doxorubicin, nipradilol, timolol, melatonin, withaferin A, bortezomib, vorinostat, tunicamycin, paclitaxel, geldanamycin, cisplatin, AZD5363 and 5-aza-2-deoxycytidine, may benefit from alpha-tocopherol succinate supplementation or/and the vitamin rich food consumption.

Alpha-tocopherol may show anti-cancer effect via the inhibition of the anti-apoptotic signaling, MAPK/ERK (Li et al. 2012). Vorinostat, ritonavir, radicicol, tamoxifen, geldanamycin, lapatinib, fulvestrant, PD98059, UO126, honokiol and SNX212, the anti-cancer drugs which target cancer cells by inhibiting the MAPK/ERK signaling may benefit from the vitamin and its rich sources, creating a synergy via the inhibition of the signaling.

That the activator protein of the inflammatory and anti-apoptotic cytokine IL-6, STAT3, is down-regulated by the pro-vitamin (Dikkan et al. 2004), may enhance the level of apoptosis in the anti-cancer treatments which administer STAT 3 and IL-6 inhibitors; S3I-201, static, STA-21, WP1066, cucurbitacin >B, 5,15-diphenylporphrin (5,15-DPP), niclosamide, auranofin, galiellalactone, kahweol, cepharanthine, SD1008, nifuroxazide, cryptotanshinone, ruxolitinib phosphate, STAT 3 inhibitor VII, sunitinib, sorafenib, bortezomib, guggulsterone, paclitaxel, honokiol, metformin, 17-AAG, vorinostat, romidepsin and tetrandrin, tocilizumab, sunitinib, sorafenib, metformin, radicicol,

17-AAg, monensin, brefeldin A, raloxifene, bortezomib, siltuximab, honokiol, curcumin, creating a synergy with the vitamin via the inhibition of STAT3 and IL-6.

One important criteria to concern in anti-cancer treatments and nutrition is the risk of contraindication of alpha tocopherol or vitamin E and anti-cancer agents that target cancer cells by producing ROS, the agents like; sunitinib, sorafenib, tetrandine, cisplatin, bortezomid, vorinostat, MG-132, metformin, thapsigargin, tunicamycin, 17AAG, DBeQ, ritonavir and brefeldin A since alpha tocopherol acts as a significant ROS scavenging agent at lower doses (Godbout et al. 2004; Donnelly et al. 1999; Yorimitsu et al. 2004 and Thews et al. 2007). If vitamin E, especially α-tocopherol would have produced more free radicals at high concentrations and would have exhibited antioxidant properties only at lower doses, like quercetin and ficetin which are pro-oxidant at 50-250 μM while they are antioxidant at only lower concentrations 0.1-20 μM (Singh et al. 2005; De Marchi et al. 2009; Robaszkiewicz et al. 2007; Gaspar et al. 1994), then the high dose vitamin E supplementations and vitamin E rich food consumption may not be contraindicated with the mentioned ROS inducing anti-cancer drugs. But, vitamin E as opposite to many other antioxidants, continues to act as an antioxidant even at its very high doses like 800, 1200 IU/d. Therefore, such high dose vitamin E supplementations or treatments may decrease the ROS concentrations produced by the mentioned anti-cancer drugs and thus, may decrease their anti-cancer potentials. The main reason for not being a pro-oxidant at high concentrations rather than being antioxidant (opposite to many other antioxidants), may be the very extraordinary and distinctive characteristic of vitamin E since it reconstructs vitamin A and vitamin C and protects many important antioxidants like vitamins C, A and B from oxidation. Under these conditions, the other re-built antioxidant vitamins by vitamin E, could have exhibited a much greater potential of antioxidation. Briefly, the excess antioxidant activities of the other antioxidants due to the vitamin E activity, may have over shadowed a possible pro-oxidant effect of the high dose of vitamin E. Unlike vitamin E, quercetin rich foods; caper, onion, cocoa powder, cranberries, cherries, green tea, black tea, broccoli, lettuce, asparagus, green pepper, berries and kale.. may not

be contraindicated with the anti-cancer drugs that kill cancer cells by producing ROS because of ROS inducing effect of quercetin. But, vitamin E rich foods/plants; soy and soy products, camelina, linseed, coconut, wheat germ, grape seed, linseed, rapeseed, sunflower and sunflower oil and maize, may better be avoided since the antioxidant effect of vitamin E even in its high doses, since it may decrease the anti-cancer potential of the mentioned ROS inducing anti-cancer drugs by its ROS scavenging activity.

Alpha-Tocopherol cuccinate may also cause an anti-cancer effect by inhibiting the anti-apoptotic signaling, ErbB2 (Wang et al. 2010). Therefore, the anti-cancer drugs which target cancer cells by inhibiting ErbB2; lapatinib, afatinib, neratinib, canertinib, sapitinib, AC480, TAK-285, CUDC-101, AEE788, tryphostin AG879, tryphostin AG825, mubritinib, SKLB1206, sorafenib, trastuzumab and saracatinib may show stronger anti-cancer potential during an anti-cancer diet, rich in alpha tocopherol or vitamin E, since the pro-vitamin like the mentioned drugs inhibit the signaling and hence may form a synergy.

The activation of the expression of PRDX3, one of the crucial genes, besides PRDX5 and Nrf1, whose down-regulation renders cancer cells sensitive to hydrogen peroxide, by alpha tocopherol, may indicate to a possible adverse effect of the provitamin if used as combined with the anti-cancer agents which kill cancer cells by producing H_2O_2; curcumin, epigallocatechin gallate, beta-carotene, sulforaphane, capsaicin and vitamin C. alpha-Tocopherol or vitamin E which decrease ROS and subsequently H_2O_2, with its scavenging activity, and inducing effect on PRDX3, may lower the concentration of H_2O_2 while making cancer cells resist to H_2O_2 by inducing PRDX3. Therefore, these antioxidant effects caused by the provitamin may decrease the anti-cancer potentials of the mentioned bio-active compounds which target cancer cells by forming the opposite effects; decreasing H_2O_2 level and inducing PRDX3 expression. Briefly; the anti-cancer drugs which target cancer cells by forming ROS and hence H_2O_2, like; sunitinib, sorafenib, tetrandine, cisplatin, bortezomid, vorinostat, MG-132, metformin, thapsigargin, tunicamycin, 17AAG, DBeQ, ritonavir and brefeldin A, may benefit from curcumin, epigallocatechin gallate, beta-carotene, sulforaphane, capsaicin and vitamin C rich foods, but not from alpha

tocopherol or vitamin E rich foods/plants. According to the current data about the association of vitamin E and cancer seems to bring an important question. While much more cohorts indicate to a possible anti-cancer effect of the vitamin, most of them administer alpha-tocopherol succinate. More research and especially cohorts are needed to highlight the relation between gamma tocopherol and tocotrienol succinate and cancer. But, under the highlight the current data, a great amount of scientific finding indicates to a significant anti-cancer effect of especially alpha-tocopherol succinate.

THE STUDIES ABOUT THE ASSOCIATION of VITAMIN E and VARIOUS TYPES of CANCER

- 29.092 men/318 pancreatic cancer/50-69 years of age/smoking adjusted, alcohol not/1985-2004/≥14.2 mg/L (0.59, 0.42-0.83, 95% CI) versus <9.3 mg/L (R:1.00, 95% CI) reduced the incidence rate (Stolzenberg-Solomon et al. 2009).
- 477 men/754 prostate cancer/40-75 years of age/1986-1996/ smoking adjusted, alcohol not/ 15.1-99.9 IU/d (1.02, 0.86-1.21, 95% CI) versus no supplementation (R:1.00, 95 % CI) did not make any change (Chan et al. 1999 (Chan et al. 1999).
- 29133 men/50-69 years of age/1985-1988/smoking adjusted, alcohol not/22 mg/dL (0.49, 0.24-1.01, 95 % CI) versus 14 mg/dL (R:1.00, 95% CI) reduced the risk of prostate cancer (Weinstein et al. 2005).
- 29.133 men/1144 lung cancer/50-69 years of age/7.7 years of follow-up/ smoking adjusted, alcohol adjusted/>13.5 mg/L(serum α-tocopherol concentration) or ≥50 mg daily α-tocopherol supplementation (0.81, 0.67-0.97, 95% CI) versus the lowest, <10.0 mg/L (R:1.00, 95% CI) α-serum tocopherol concentration) reduced the risk (Woodson et al. 1999).
- 27.168 women/1985-1997/49-65 years of age/smoking and alcohol not adjusted/30.02 mg/L (as the highest quartile of serum α-tocopherol concentration (1.4, 0.7-2.6, 95% CI) versus the lowest (R:1.00, 95% CI) did not make any change for the risk of breast cancer (Hulten et al. 2001).
- 96.382 men/467 prostate cancer/45-75 years of age/1993-1996/ smoking adjusted, alcohol not/2.51 mg/dL/the highest quartile of α-tocopherol serum concentration (0.95, 0.65-1.41, 95% CI) versus the lowest quartile ((≤0.90 mg/dL) (R:1.00, 95% CI) did not make any change(Gill et al. 2009).
- 137.001 men/966 prostate cancer/60 years of medium age/ smoking adjusted, alcohol adjusted/≥1680 μg/dL as the highest

quartile of serum α-tocopherol concentration (0.82, 0.61-1.11, 95% CI) versus <1132 μg/dL as the lowest (R:1.00, 95% CI) did not make any change (Key et al. 2007).

- 10.456 men/1974-1996/45-64 years of age/smoking adjusted, alcohol not/the highest quartile of serum α-tocopherol concentration, 1.6 mg/dL(0.31, 0.11-1.06, 95% CI) versus the lowest, 1.1 mg/dL(R:1.00, 95% CI) reduced the risk. More importantly the chemothrepeutic effect of gamma-tocopherol, 0.30 mg/dL (0.21, 0.08-0.54, 95% CI) versus the lowest, 0.17 mg/dL (R:1.00, 95% CI), was greater than α-tocopherol (Huang et al. 2003).
- 18314 men and women/278 lung and 205 prostate cancer/45-74 years of age/5 years of follow-up/alcohol adjusted, smoking adjusted/the highest quartile, 13900 ng/mL(0.52, 0.31-0.88) versus the lowest, ≤12900 ng/mL (R:1.00, 95% CI) decreased the risk of lung and pancreas cancer(Goodman et al. 2003).
- 22.071 men/40-84 years of age/smoking adjusted, alcohol adjusted/the highest quartile of serum α-tocopherol concentration, 14.441 ng/mL(1.06, 0.76-1.48, 95% CI) versus the lowest, 8564 ng/mL(R:1.00, 95% CI) decreased the risk of prostate cancer(Gann et al. 1999).
- 18.314 men/778 prostate cancer/smoking adjusted, alcohol not/60.6 years of medium age/5 years of follow up/the highest quartile of serum α-tocopherol concentration, 37.1 μmol/L (0.82, 0.61-1.10, 95% CI) versus the lowest, <23.0 μmol/L(R:1.00, 95% CI) reduced the risk of prostate cancer(Cheng et al. 2011).
- 4060 men asbestos workers, 14254 men heavy smokers/45-69 years of age/alcohol adjusted, smoking adjusted/15 years of follow up/α-tocopherol serum concentration, 16792 ng/mL(0.59, 0.34-1.04) versus 10666 ng/mL(0.72, 0.42-1.22), Υ-tocopherol serum concentration, 3567 ng/mL(0.91, 0.52-1.59) to 1754 ng/mL(0.86, 0.50-1.48) decreased the risk of prostate cancer (Goodman et al. 2003).
- 29133 men smokers/6.1 years of follow up/50-69 years of age/ alcohol adjusted, amoking adjusted/<11.5 mg/L α-tocopherol serum concentration (R:1.00, 95% CI) to ≥ 10.3 mg/L(0.31,

0.66-0.77) and <10.3 mg/d vitamin E intake(R:1.00, 95% CI) to ≥10.3 mg/d(0.56, 0.13-0.38) decreased the rsk of prostate cancer(Heinonen et al. 1998).

- 2974 men/87 lung cancer/30 prostate cancer, 28 stomach cancer, 22, colon cancer/17 years of follow up/plasma vitamin E concentration, ≥36.5 μmol/L(0.86, 0.57-1.28) to <36.2 μmol/L (R:1.00, 95% CI) decreased the risk of all the mentioned types of cancer(but vitamin E was evaluated as combined with vitamin C, retinol and carotene, not separately!)/smoking adjusted, cholesterol adjusted, alcohol not/49-63 years of age (Eichholzer et al. 2000).
- 41837 women/76 upper respiratory tract cancer/55-69 years of age/1986-1992/smoking adjusted, alcohol adjusted/<2.01 mg/d (R:1.00, 95% CI) versus >2.93 mg/d (0.8, 0.3-2.0, 95% CI) decreased the risk (but the form of the vitamin is not written in the published study!) (Zheng et al. 1995).
- 11178 women/761 ovarian cancer/67-105 years of age/1984-1993/ alcohol adjusted, smoking adjusted/≥100 IU/d (0.78, 0.50-1.23, 95% CI) versus no supplementation (R:1.00, 95% CI) decreaed the risk (Losonczy et al. 1996).
- 34387 postmenopausal women/879 breast cancer/1986-1992/ alcohol adjusted, smoking not/≥35.66 IU/d (0.97, 0.78-1.21, 95% CI) versus <5.66 IU/d (R:1.00, 95% CI) decreased the risk(but the form of the vitamin is not mentioned in the published paper!) (Kushi et al. 1996).
- 299 women/224 breast cancer/20-69 years of age/3 years of follow up/ smoking adjusted, alcohol not/<6.26 mg/d (R: 1.00, 95% CI)versus ≥12.71 mg/d(0.81, 0.44-1.88, 95% CI) did not make any effect(the form of the vitamin during supplementation is not mentioned in the published paper!)(Do et al. 2003).
- 36265 men and women/766 various cancers/8 years of follow up/smoking adjusted, alcohol not/>20.2 μmol/L (1.7, 1.1-2.7, 95% CI) plasma α-tocopherol concentration in men versus 18.3 μmol/L (R:1.00, 95% CI) decreased the risk in both sex (Knekt et al. 1991).

- 120852 men and women/282 gastric carcinoma/55-69 years of age/smoking adjusted, alcohol adjusted/1986-1993/21.70 mg/d(0.8, 0.5-1.2, 95% CI) versus 6.59 mg/d (R:1.00, 95% CI) did not make any effect (Botterweck et al. 2000).
- 47780 male smokers/1896 smokers with prostate cancer/1986-1996/40-75 years of age/smoking adjusted, alcohol not/≥100 IU/d(1.07, 0.95-1.20, 95% CI) versus no supplementation(R:1.00, 95% CI) decreased the risk(Chan et al. 1999).
- 991522 men and women/1289 bladder cancer/1982-1998/<40-80≤years of age/10 years of follow up/smoking adjusted, alcohol not/the vitamin supplementation daily(0.60, 0.37-0.96, 95% CI) versus no supplementation(R:1.00, 95% CI) decreased the risk (but the form and dose of the vitamin are not written in the published paper(Jacobs et al. 2002).
- 1548 women/820 breast cancer/49-61 years of age/3 years of follow up/alcohol adjusted, smoking not/≤5.2 IU/d (0.71, 0.48-1.05, 95% CI) versus >8.6 IU/d (R:1.00, 95% CI) decreased the risk(Bohlke et al. 1999).
- 89494 women/1439 breast cancer/34-59 years of age/8 years of follow up/alcohol adjusted, smoking not/≥24.1 IU/d(0.88, 0.69-1.10, 95% CI) versus <3.9 IU/d (R:1.00, 95% CI) did not make any effect(Hunter et al. 1993).
- 623573 women/650 breast cancer/4.3 years of follow up/alcohol adjusted, smoking not/19.82 mg/d(1.25, 0.85-1.85, 95% CI) versus 5.96 mg/d(R:1.00, 95% CI) did not make any effect(but the age and form are not written in the published paper(Verhoeven et al. 1997).
- 167447 women/212 colon cancer/5 years of follow up/vitamin E supplementation (0.44, 0.28-0.71, 95% CI) versus no use of supplementation (R:1.00, 95 % CI) decreased the risk(but the form and dose are not written in the published paper(Bostrick et al. 1993).
- 139 women, 57 women with breast cancer, 30-66 years of age/ 10.3 mg/d vitamin E intake (2.14, 0.95-4.83, 95% CI) versus 5.8

mg/d (2.32, 1.20-4.48, 95% CI) decreased the risk/alcohol and smoking adjusted (Shahar et al. 2008).

- 132837 men and women, 267 with liver cancer, 40-74 years of age/4 years of follow up/ >16. 176 mg/d (0.60, 0.40-0.89, 95% CI) versus ≤9.977 mg/d (R:1.00, 95% CI) decreased the risk/ smoking and alcohol adjusted (Zhang et al. 2012).
- 1295 postmenopausal breast cancer, 50-74 years of age/5.8 years of age/≥55 nmol/L (1.55, 1.00-2.39) as the highest serum 25(OH) D concentration versus to 10 nmol/L (1.14, 1.05-1.24) as the lowest serum 25(OH)D concentration decreased the risk/alcohol and smoking not adjusted) (Vrieling et al. 2011)
- 50-69 years of age/number of lung cancer: 433/the highest α-tocopherol serum concentration:14.2 mg/L versus 11.5 mg/L did not make any change/14.564 men and women/smoking adjusted, alcohol not (The alpha-tocopherol, beta carotene cancer prevention study group. 1994).
- 50-69 years of age/6.1 years of follow up/50 mg/d α-tocopherol supplementation in men with leisure activity (0.7, 0.5-0.9, 95% CI) versus sedentary (RR: 1.0)/decreased the risk for prostate cancer /29.133 men/smoking adjusted, alcohol not/317 prostate cancer (Hartman et al. 1998)
- 22805 men/208 liver cancer/24 years of follow up/ the highest quintile of serum α-tocopherol (15.3 mg/L (0.55, 0.35-0.86, 95% CI) versus lowest quintile (8.6 mg/L, RR: 1.00) did not make any change for liver cancer/smoking adjusted, alcohol not (Lai et al. 2014).
- 370.000 men/4004 prostate cancer//the highest quintile of serum alpha tocopherol content (21.68 mg/mL)(0.82, 0.61-1.10, 95% CI) versus the lowest quintile (0.32 mg/mL) (0.57, 0.31-1.06)/ decreased the risk (but alpha tocopherol, not ϒ-tocopherol !!)/ 13 years of follow up (Cui et al. 2014).
- 50-74 years of age/ 86.404 men/4281 prostate cancer/ 7 years of follow-up/ the highest quintile of vitamin E (≥400 IU/d) (0.96, 0.74-1.24, 95% CI) versus the lowest (none) (R: 1.00) reduced the risk of prostate cancer in current smokers/smoking adjusted, alcohol not (Rodriguez et al. 2004).

- 50-76 years of age/35.242 men/smoking and alcohol adjusted/80 prostate cancer/10 years of follow up/10 times/week vitamin E supplementation with the mix of α, β, Υ, δ tocopherol (0.16, 0.75-1.1, 95% CI) versus none (R: 1.00, 95% CI) reduced the risk of prostate cancer (Peters et al. 2008).
- 40-59 years of age/56.837 women/519 breast cancer/5 year of follow-up/the highest quintile of alpha-tocopherol intake, 7 mg/d (1.37, 0.81-2.33, 95% CI) versus the lowest quintile, <3 mg/d (R: 1.00, 95% CI) reduced the risk of breast cancer/smoking and alcohol adjusted (Rohan et al. 1992)

The Association of Reactive Oxygen Species (ROS) with Cancer

A free radical is any species which contains one or more unpaired electrons (Halliwell and Gutteridge, 1984). The unpaired electron makes the free radical more reactive. Reactive Oxygen Species (ROS) are generated by oxydant enzymes, phagocytic cells and ionizing radiation. Superoxide anion ($O_2^{\cdot}$) is the first free radical, formed by the electron transport chain when O_2 picks up a single electron. Other ROS like hydroxyl (OH), perhydroxyl (HO_2) and hydrogen peroxide (H_2O_2) are formed by the superoxide anion ($O_2^{\cdot}$) (Nappi and Vass, 1998). The superoxide anion ($O_2^{\cdot}$) enters into a reaction to form H_2O_2 by the enzyme superoxide dismutase (SOD). H_2O_2 is not reactive enough to cause damage on cell, but it can cross the cell membrane and form highly reactive and thus very harmful hydoxyl radical (OH) by interacting with metals such as Fe^{2+} and Cu^{+}. The elevated levels of modified bases in DNA like the substitution of CC to TT (Reid and Loeb 1993), which results in cancer may be due to the large amount of H_2O_2 production. Briefly, the free oxygen radical species are concerned as one of the initial and strongest factors that initiate cancer in human (Ames et al. 1993; Poulsen et al. 1998). Here, the formation of the reactive and harmful hydroxyl radical (OH) from harmless H_2O_2, is one of the most critical points that indicates to the role of antioxidants and antioxidant rich foods, especially fruits and vegetables since H_2O_2 can be neutralized by the enzymes, catalase and glutathione peroxidase. Thus, any food rich in catalase or glutathione peroxidase may contribute to prevent from cancer. This means that the rich sources of catalase and/or glutathione such as wheat sprouts (Marsili et al. 2004), potato (Spychalla and Desborough 1990), carrot (Baardseth and Slinde 1983), Onion (Lee et al. 2012), garlic (Perchellet et al. 1986), Broccoli (Davis et al. 2002), Brussels sprouts (Sorensen et al. 2001; Hoelzl et al. 2008), cabbage, sweet potato, daikon (Hossain et al. 2013), pumpkin (Nkosi et al. 2006), Avocado (Mahmoed and Rezq 2013), spinach (Sheptovitsky and Brudviq 1996) may show an anticarcinogenic potential due to their

inhibitory effect on H_2O_2(The references in parentheses are the authors and their teams which found the mentioned effect of the mentioned food). The protein, catalase, has a 3D structure in its active form and a heme group. The neutralization of ROS starts with the oxidation of Fe (III) to amore oxidized form Fe (IV) in the heme group of catalase releasing H_2O and oxygen. In the second part of the neutralization with catalase, the second molecule of H_2O_2 is converted back into water by the effect of oxygen while reducing Fe (IV) back to Fe(III). Briefly, catalase breaks down H_2O_2 into water and oxygen, preventing the harmful free radical, hydroxyl (OH) which mutates the DNA plasmid (Khan et al. 2005), like its damage on thymidine 5-monophosphate (TMP) (Ahmad et al. 2009; Hussain et al. 2003).

H_2O_2+Fe(III)-catalase ⟶ H2O+O=Fe(IV)-catalase(+)
H_2O_2+O=Fe(IV)-catalase(+) ⟶ H_2O+Fe(III)-catalase+O_2 (Ali, 2009)

Reactive Oxygen Species (ROS) have been reported to play role in both apoptosis and cancer. These species which are derived from the metabolism of molecullar oxygen such as superoxide anion radical (O_2^-), singlet oxygen ($^1O_2$), hydogen peroxide (H_2O_2) and the highly reactive hydroxyl radical (OH) form in excess amount when the critical balance is distrupted like the ROS formation during stress and the formation of these species because of the foods rich in oxidants and the depletion of antioxidants. In living cells, the major source of endogenous ROS are hydrogen peroxide and superoxide anion which are generated naturally as by products of cellular metabolism like mitochondrial respiration (Nohnl et al. 2003). Hydrogen peroxide which is one of the initial carcinogens may be converted into water by the enzymes, catalase or glutathione peroxidase. Thus, any change in the expression of these enzymes can significantly increase the amount of ROS. These harmful molecules can cause DNA damage by reacting with nucleotides which may initiate cancer (Ahsan et al. 2003).

Glutathione peroxidase catalyzes the reaction between its selenol group (RSeH) in selenocyteine of glutathione (GSH) and H_2O_2 which yields seleninic acid (RSeOH) to be converted to glutathione disulfite

(GS-SG) via to several reactions. Finally, glutathione disulfite enters into reaction with NADPH to be converted back to glutathione. Briefly, glutathione peroxide eliminates the harmful carcinogenic radical, OH, by using selenium (Bhabak and Mugesh 2010).

$RSeH+H_2O_2 \longrightarrow RSeOH+H_2O$
$RSeOH+GSH \longrightarrow GS\text{-}SeR+H_2O$
$GS\text{-}SeR+GSH \longrightarrow GS\text{-}SG+RSeH$
$GS\text{-}SG+NADPH+H^+ \longrightarrow 2GSH+NADP^+$

Are Free radicals cancerogenic or anticancerogenic?

With the current knowledge as related to the effects of free radicals on cancer, it seems clearly that free radicals (reactive oxygen species, ROS) have got completely two different effects, either cancerogenic or anticancerogenic. Cancerogenic effect of the radicals is derived from their destructive effect in addition to the destruction of tumor cells by the anticancer drug. Other words, free radicals (ROS) may enhance the harmful and destroying effects of the anticancer drugs which kill tumor cells by producing free radicals. Many of the important anticancer drugs commonly applied in cancer treatments presently show their anticancer effect by producing free radicals and killing tumor cells by these free radicals. Thus, a question of 'might a candy or a fatty food or fat and sugar unexpectedly show an anticancer effect by increasing the free radical production capacity of these anticancer drugs, since they are the actual free radical producers?'. This appears a hypothesis which may be correct especially when the anticancer effect mechanism of the most of today's anticancer drugs by producing free radicals which are harmful for cancer cells with its present samples below is considered.

Isorientin, one of the anticancer drugs, induces apoptosis in human hepatoblastoma cancer (HepG2) cells by producing and increasing reactive oxygen species, and then suppressing PI3K (phosphatidylinositol-4,5-bisphosphate 3-kinase), the intracellular signal transducer enzyme which is capable of phosphorylating inositol for its activation (Yuan et al. 2014). Inositol hexaphosphate (IP-6) is a naturally occurring polyphosphorylated carbohydrate, abundantly present in many plant sources and in high-fiber diets such as cereals and legumes. The substance is important in regulating the vital cellular functions like signal transduction, cell proliferation and differentiation. The substance has also been recognized with its antioxidant potential in cancer prevention and control of experimental tumor growth, progression and metastasis. It also contributes to lower elevated serum cholesterol and calcification, enhance immune system and reduce pathological

platelet activity all of which may decrease the risk of cancer (Vucenik and Shamsuddin 2006). On the other hand, the transitions that control normal cell cycles which are altered in tumor cell cycles have its own molecular targets, one of which is cyclin-dependent kinase family, the family of enzymes whose members are dependent on a protein, cyclin, and give the cell exquisite control over decisions to progress from one cell cycle phase to the next (Deshpande et al. 2005), like regulating intracellular Ca^{2}+ release and Ca^{2}+ dependent signaling events in breast cancer (Soghoian et al. 2005). During cancer, the suppression PI3K in cancer cells, like in healthy cells, cause an opoptosis by increasing Ca^{2}+ release, inhibiting inositol activity while increasing platelet activity and elevating cholesterol and calcification due to the inositol inactivation. The critical point here is triggering effect of the reactive oxygen species which cause to the suppression of PI3K and as a result, apoptosis. Briefly, isorientin as one of the important anticancer drugs has its anticancer effect by producing free radicals.

Bax is the protein encoded by Bax gene, proapoptotic Bcl-2 protein family. The protein inhibits superoxide production and the peroxidation of cardiolipin, an important component of the mitochondrial membrane (Jiang et al. 2008). But, the absence of Bax, the ROS inhibitor, strongly inhibits p53 (the tumor suppressor gene) and induces the generation of reactive oxygen species and thus causes apoptosis (Macip et al. 2003). It seems clear that the rate of the free radicals regulates the activation of p53 via to Bax protein and appears as one of the main anticancer effects of p53.

PRKD, the DNA-dependent protein kinase catalytic subunit and the enzymes which act as molecular sensor for DNA damage, are vitally important for the repair of the damage in DNA. This gives an important role to PRKD by protecting the structure of DNA from any mutation. But, the activation of the enzymes was also shown to mediate the ROS-induced autophagy (Eisenberg-Lerner and Kimchi 2012) which indicates to a close link between the free radicals and these enzymes. Similarly, MAPK8, mitogen-activated protein kinase 8 (also known as JNK1), is the enzyme that is encoded in humans by the MAPK8 gene and the enzyme triggers tumor formation by decreasing the level of Bcl-xl, the pro-survival protein contributing to apoptosis. But, the activation of

the kinase by tumor-necrosis factor alpha (TNF-α) is also required for TNF- α-induced apoptosis. Both the TNF- α activated MAPK8 and the other activated members of MAPK family causes apoptosis in human pancreatic cells pretreated with oxidant benzy-isothiocyanete by the generation of the reactive oxygen species (Ravi et al. 2009). Here, another example of the apoptosis via to PRDK, MAPK8, Bcl-xl and TNF- α seems to appear due to the formation of reactive oxygen species.

The receptors which take the signals to induce apoptosis are vitally important in tumor inhibition and destruction. One of the receptors that take such signals, TNF receptor I, triggers the generation of reactive oxygen species via the mitochondria, leading to the activation of caspase, ASK1 (kinase 1), a MAPK (Mitogen Activated Protein Kinase) which activates another MAPK, p38, while decreasing the level of Bcl-xl protein (Beta Cell Lymphoma Extra Large), the member of the Bcl-2 proteins which acts as a pro-survival protein in the mitochondria by preventing the release of mitochondrial contents (Schulze-Osthoff et al. 1993; Liu et al. 2000 and Grethe et al. 2004). Like the examples above, TNF, as one of the important tumor suppressors with these findings, appears to inhibit tumorogenesis in the same way, producing reactive oxygen species. The intracellular protein serine/threonine kinases which are called as mitogen activated protein kinases (MAPKs) such as ERK1, ERK2 and p38 are activated in response to diverse extracellular stimuli such as microorganisms, radiation and toxins and by protooncogene-encoded proteins that induce proliferation. Hence, the kinases have emerged as the important pathways in signaling of cancer and the targets in the preparation of the new generation of anticancer drugs (Sebolt-Leopold 2000). Here, TNF may be in a cancer promoting effect by activating these cancer inducers in the early steps but then, the activations of these enzymes and caspase result in Ca^{2+} influx, mitochondrial depolarization and the release of cytochrome c (a small hemeprotein associated with the inner membrane of the mitochondrion) all of which cause apoptosis (Sharma and Rohrer 2004).

P66Shc, a proto oncogene Src homologous collogen homologue (Shc) adaptor protein, is vitally important in mediating receptor tyrosine kinase signaling (Rajendran et al. 2010). The activity of tyrosine kinase in tumor cells, like in normal cells, has an uppermost importance since

the enzyme transfers a phosphate group from ATP to a protein in the cell. So, it functions as an 'on' or 'off' switch in many cellular functions. Thus, the mentioned function makes the enzyme as vitally important in the proliferation of tumor cells similar to its effect on the normal cell proliferation. The mediation of the receptor tyrosine kinase signaling by p66Shc gives a privileged role and importance to p66Shc protein kinase because it determines the activity level of tyrosine kinase. The same protein was informed to inhibit RKO colon carcinoma cell in mice (Galimov et al. 2012) while decreased levels of proapoptotic protein have been found in human lung cancer and malignant ovarian surface epithelial cells (Du et al. 2013; Zheng et al. 2013 and Abdollahi et al. 2003). This proapoptotic protein with its mentioned potential to respond to energy status changes and regulate mitogenic signaling protein shows its apoptotic effect as a response to oxidative stress (Lebiedzinska-Arciszewska et al. 2015). Another important finding about the close relation between the reactive oxygen species and the apoptosis by the effect of the protein is via to the naturally occurring phenethyl isothiocyanate (PEITC). PEITC treatment of PC-3 and LNCaP human prostate cancer cells increases Ser36 phosphorylation of p66Shc which increases its binding with Pin 1, a protein-coding gene in cell proliferation. The binding of p66Shc with Pin 1 promotes translocation of p66Shc to the mitochondria. The p66Shc protein localized to the mitochondria is released from HSP70, a molecular chaperon and finally causes the production of reactive oxygen species leading to caspase-3 activation and apoptotic cell death due to the reactive oxygen species (Xiao and Singh 2010). The protein which was informed as having the similar oxidative effect with its production of reactive oxygen species by another study (Beltrami et al. 2013) emerges with its possible clinic use to induce apoptosis by producing reactive oxygen species during cancer, opposite to a human without cancer whose body's oxidation should have been inhibited including the inhibition of p66Shc and the production of reactive oxygen species by this protein. Lck is a kinase which is important in T-cell apoptosis and the proapoptotic activity of p66Shc. Furthermore, p66Shc phosphorylation on serine 36(S36), an event on which the proapoptotic function of p66Shc depends requires Lck and CaMKII, a Ca^{2+}/calmodulin-dependent kinase (Patrussi et al.

2012). Another anticancer effect via to reactive oxygen species and P66Shc includes another kinase, Lck, which causes p66Shc phosphorylation on serine 36 to start the proapoptotic function of p66Shc (Gruber et al. 2004). As a result of the phosphorylation and then activation of the protein, p66Shc produces reactive oxygen species which kill tumor cells and induce apoptosis. Similarly, Toxol and dichloroacetic acid (DCA), in spite of the risk of nephrotoxicity, induce apoptosis and show anticancer effect by activation p66Shc which results in the production of the reactive oxygen species that kill cancer cells (Arany et al. 2013). On the other hand, naturally occurring phenethyl isothiocyanate (PEITC) in cruciferous vegetables was informed to suppress growth and induce apoptosis by increasing the level of Ser36-phosphorylated p66Shc resulted in the translocation of the protein to mitochondria in PEITC-treated prostate cancer cells (Xiao and Singh 2010) which starts reactive oxygen species to kill the tumor cells. The same compound is an antioxidant and apoptotic on cancer cells by inducing phase II detoxification enzymes. First, phase 1 enzymes begin the detoxification process by chemically transforming lipid soluble compounds into water soluble compounds in preparation for phase II detoxification. The transformation is performed by a family of enzymes, cytochrome P450s. But, in many cases, products from the phase 1 reactions have been rendered more reactive than the original toxins which make them more destructive than they once were. Additionally, phase I reactions are not sufficient to make toxins water-soluble enough to complete the excretion. So, the phase II enzymes both increase the solubility of these toxic compounds and reduce their toxicity. The production of most phase II enzymes is controlled by a protein called nuclear factor erythroid-derived 2 (Nrf2), the master regulator of antioxidant response. Nrf2 is inactive under normal cellular conditions, however oxidative stress and its reactive oxygen species activate the protein and then the protein turns on the genes of many antioxidant proteins, including phase II. Briefly, reactive oxygen species triggers an antioxidant response. Any antioxidant during the treatment of the anticancer drug may interfere with the treatment since the anticancer drug kills the tumor cells by producing reactive oxygen species. Neither the overexpression of Nrf2 nor any other antioxidant interference during

the treatment with the anticancer drug may limit the tumor killing potential of the drug. But unexpectedly, oxidant food components rather than antioxidant may be beneficial to enhance the tumor killing effect of the anticancer drug in the treatments during cancer since the ratio of the reactive oxygen species to kill the tumor cells might have been increased with this approach. According to the findings mentioned above, there may be a great possibility that the reactive oxygen species from the foods with a high rate of oxidation capacity like the fatty foods, fried, cured or candy ones may produce reactive oxygen species and these reactive oxygen species may join to the reactive oxygen species produced by the anticancer drug to kill the tumor cells, enhancing the anticancer and apoptotic effect of the anticancer drug provided that such foods are consumed during the time of the treatment with the anticancer drug. There may be no need to worry about the damage of too much reactive oxygen species on healthy cells besides tumor cells since the antioxidant response like the activation of the antioxidant gene, Nrf2, will be given by the same reactive oxygen species. That the production of reactive oxygen species by the anticancer drug or the food taken during the treatment in cancer period activate the protein, Nrf2, may be helpful to prevent the damage of the reactive oxygen species on healthy cells in the later stages of the cancer treatment with the anticancer drug. But, the time period to benefit from the antioxidant gene should not be the treatment period which administers anticancer drug. Because, the antioxidant gene appears as the main factor to increase the resistance against apoptosis with its inhibitory effect on the reactive oxygen species during cancer while it may induce apoptosis by increasing immune defence and its fight against tumor cells decreasing the chance for the damage of cell nuclei by reactive oxygen species which may cause cancer during the time period without cancer. One of the surprising findings which support the hypothesis of avoiding the antioxidant during the treatment with the anticancer drug is the elevated expressions of the antioxidant gene, and some other antioxidant enzymes such as SOD1 and SOD2, the enzymes that catalyze the dismutation of the toxic superoxide ($O2^{-}$) radical into molecular oxygen (O_2) or hydrogen peroxide (H_2O_2) and Bcl-2 and Bcl-xl, the antiapoptotic proteins, in the cadmium-transformed human lung bronchial epithelial BEAS-2B cells

while the level of reactive oxygen species is extremely low (Son et al. 2014). But, in contrast the normal healthy period without cancer may use the benefits of the antioxidants such as Nrf2. The activators of the gene in the foods like broccoli and other cruciferous vegetables does not only activate Nrf2 but also suppresses cellular accumulation of an important carcinogen, arsenic while detoxifying another group of carcinogens, aflatoxins and air-borne toxins (Shinkai et al. 2006; Kensler et al. 2013), in healthy individuals. On the other hand, the knockdown of Nrf2 attenuates sulforaphane induced heme oxygenase-1 (HO-1), the human gene that encodes for the enzyme heme oxygenase 1 which cleaves heme to form biliverdin, the substance with an antioxidant and anti-mutagenic effect (Lee and Lee 2011). The other anti-inflammatory and anticancer effects of the Nrf2 activator, sulforaphane, are due to the reduction in NF-kB (nuclearfactor kappa-light-chain-enhancer of activated B cells), a protein whose incorrect regulation is linked to cancer and inflammation since it controls the transcription of DNA, abrogation of inducible nitric oxide synthase (iNOS) and cyclooxcygenase-2 (COX-2) expressions and decrease in tumor necrosis factor-α (TNF- α) and interleukine-6 (IL-6) levels (Negi et al. 2011), briefly, the enzymes and cytokines all of which contribute to cancer. The enzyme, cyclooxygenase-2 (COX-2) regulates prostaglandin synthesis and its overexpression contributes to several epithelial cancers by triggering angiogenesis and tumor cell invasiveness (Sinicrope and Gill 2004), converting arachidonic acid to prostaglandin H-2 which activates macrophages, oncogenes, inflammatory cytokines and growth factors, briefly the potent tumor promoters (Singh and Lucci 2002). But, COX-2 is the particular prostacylin, a member of prostaglandins which is naturally found in blood vessel lining which relaxes or unsticks platelets. So, the anticancer drugs that inhibit COX-2 expression, like celecoxib and other coxibs, increase the risk of cardiovascular diseases due to clotting (Funk and FitzGerald 2007; Martinez-Gonzales and Badimon 2007; Hara and Kudo 2006). But, curcumin (10-15 micromol/L) of turmeric from the ginger family (*Zingiberaceae*) enhances the anticancer effect of celecoxib by inhibiting COX-2, without the mentioned side effect of the drug by allowing its use in a very low dose (5 micromol/L) (Lev-Ari et al. 2005). The decrease in cyclooxygenase-2

expression and the apoptosis due to the decrease is always accompanied with the ROS formation. Confirming this, the green tea catechin epigallcatechin-3-gallate (EGCG) on colon cancer cells induces apoptosis and abolishes cell proliferation in the presence of H_2O_2, accompanied by the activation of AMP-activated kinase (which leads to oxidation and ROS formation) and decrease in cyclooxygenase-2 expression, but the apoptotic effect diminishes when the colon cancer cells are treated with the ROS scavenger NAC (N-acetyl-1-cysteine) (Park et al. 2009).

Bromelain in cancer and its relation with ROS

Bromelain belongs to a group of protein digesting from the fruit or stem of pineapple. It refers to a mixture of different thiol endopeptidases, phosphatase, glucosidase, peroxidase, cellulose, escharase (the non-proteolytic enzyme in pineapple stem which is often administered to remove the necrotic and infected material from a wound) and several protease inhibitors. Bromelain also possesses anticancerous activities and promotes apoptotic cell death (Pavan et al. 2012). One of the important food substances with anticancer effect, bromelain, shows its effect on cancer by inhibiting COX-2 activity similar to sulphoraphane tough it has got many other mechanisms for its anticancer effect. The enzyme was shown to inhibit COX-2 in human monocytic leukemia and murine microglial cell lines (Huang et al. 2008; Hou et al. 2006). The ezyme as combined with N-acetylcysteine also diminutes cyclins A, B and D (indispensable elements of the cell cycle whose derangement lead cancer), the emergence of the immunoreactive subunits of caspase-3, caspase-7 and caspase-8 which may result in enhanced tumorigenic potential. But, the same proteases are anticancer under normal circumstances, without the emergence of their subunits, can reduce the expression of anti-apoptotic Bcl-2 and pro-survival phosphor-Akt, deregulate the autophagy-related proteins, namely Atg3, Atg5, Atg7, Atg12 and Beclin 1 (Amini et al. 2014). Similar to many other anticancerogen food substances, bromelain generates the reactive oxygen-species in human epidermoid carcinoma-A431 and melanoma-A375 cells (Bhui et al. 2012) followed by mitochondrial membrane depolarization while it induces apoptosis. One reason for the increase in ROS (Chobotova et al. 2010) by bromelain may be due to the activation of neutrophils that ROS are the intracellular regulators of functional activity in the cells (Fialkow et al. 2007; Wu et al. 2008). The increase in ROS by bromelain should be considered in cancer treatments by anticancer drugs. Especially, two factors seem important with the current findings that first, bromelain in tablet form or in food should be taken as combined with the foods rich

in oxidant capacity rather than antioxidant like fatty foods, fried foods of the foods rich in starch or glycogen since bromelain and such foods in addition to some anticancer drugs produce ROS and kill tumor cells with the ROS. The second is the 'form' of bromelain that bromelain with its native form in foods show less anticancerogenic effect since it is not stable in the acidic conditions of gut. But, its encapsulated nanoparticles in poly lactic-co-glycolic acid, PLGA, may be very promising for its use in oral chemotherapy with its greater stability in the same conditions (Priyanka et al. 2014). This increase in ROS by bromelain may enhance the anti-cancer effect of the drugs, cisplatin and 5-FU (Pillai et al. 2013). Bromelain administarion during the cisplatin treatment may decrease the side effect, the risk of cardiovascular disease due to too much inhibition on COX-2 by the drug, in case of its use (75 μg/mL) as combined with NAC (N-acetyl cystein) and cisplatin, lowering the dose of the drug to only 0.1 mM which results in less toxicity and the lower risk of the mentioned side effect, but with a greater apoptotic effect (Pillai et al. 2013). The synergism of bromelain with the drugs also reveals another anti-cancer effect mechanism of the enzyme complex that bromelain, like cisplatin and 5-PU, adversely affects MUC1, a glycoprotein that provides tumor cells with invasive, metastatic and chemo-resistant properties. The maximum concentration of the enzyme complex is exist in stem of the fruit which necessitates its extractrion (Heinicke and Gortner 1957). Therefore, the involvement of the stem, tough it is hard in texture, followed by a softening procedure in warm water and then grinding may be advisable for the nutrition of the patients with cancer during the treatment with the anti-cancer drugs, especially the ones; cisplatin and 5-PU.

Simian Vacuolating Virus 40 (SV40) Tag is a protein and a proto-oncogene derived from the polyomavirus SV40. As the 'poly' means many and 'oma' means tumor, the virus has an ability to cause many types of cancers. One of the close relations of the virus protein (SV40) is due to the fact that it has telomerase activity. The telomere is a repetitive stretch of DNA found to each end of a chromosome. Telomeres are shortened when a cell divides. But, an enzyme, telomerase, extends the telomere without limit and cancer cells can divide without any limit since such cells have often telomerase activity. On the other

hand, the p53 and the retinoblastoma (Rb) genes are tumor suppressor. These genes promote cell-cycle arrest when the cells are injured or damaged. The activity of the genes is critical to stop cell proliferation, other words, tumor formation. The SV40 oncoprotein binds to these anti-cancer genes and inactivates them like in many cases of cancer. Protein phosphatase 2A (PP2A), the enzyme that plays a role in protein synthesis, DNA replication, transcription and metabolism, comprises 174 amino acids. The 97th and 103th amino acids in SV40 interact with PP2A which reduces the ability of PP2A to inactivate the apoptotic proteins, ERK 1 and MEK 1, resulting in cell proliferation (Sontag 1993). SV40 protein also alteres the expression of the tumor suppressor gene, RASSF1A, while inactivating another apoptotic gene, Notch-1 by overexpressing the gene which results in cell proliferation. Finally, SV40 contributes to tumor formation by activating the cell growth promoters; hepatocyte growth factor (HGF) receptor and the insulin-like growth factor (IGF). Bromelain may show one of its anticancer effect by eliminating the cancerogens, human papilloma virus (HPV) including SV40 although presently, there seems only one study which has been performed as related to the relation between bromelain and SV40, showing the digestion of the cancerogen virus by bromelain protease (200IU) (Mistry et al. 2007).

One of the anti-cancer effect of the enzyme may be due to its proteolytic action which dissolves fibrin. Cancer cells hide under a cloak of fibrin to escape but when they are uncloaked by the proteolytic effect of bromelain on fibrin, these cells can be spotted and attacked by immune system. Fibrin also sticks cancer cells to each other which increase the chance for metastases (Chakraborty 2015).

The current status of SULFORAPHANE and cancer relation

Sulforaphane, one of the anti-cancer food substances, is a molecule within the isothiocyanate (the chemical group, -N=C=S, formed by substituting the oxygen in the isocyanate group, R-N=C=O, with a sulfur) group of organosulfur compounds. The isothiocyanate, the origin of sulforaphane, is produced by the hydrolysis of glucosinolates by the plant enzyme myrosinase (Holst and Williamson 2004).

The richest sources of sulforaphane and other glucosinolates are the cruciferous or Brassica vegetables, including broccoli, Brussels sprouts, cabbage, cauliflower, collard greens, kale, kohlrabi, mustard, rutabaga, turnips, bok choy and Chineese cabbage (Kristal and Lampe 2002).

Most of the glucosinolates including sulforaphane are chemically and thermally stable. Furthermore, enzymatic hydrolysis for the formation and activation of the glucosinolates is required since myrosinase, the enzyme-ß-thioglucosidase, comes in contact with glucosinolates and catalyzes the hydrolysis of the glucosidic bond, yielding the stable isothiocyanates like sulforaphane at neutral pH (6-7). Therefore, the crucial point which should be taken into consideration in cancer nutrition is the necessity of a grinding or chopping of the cruciferous vegetables in pre-cooking step in cancer. Additionally, a thorough chewing of the cruciferous vegetables should always be adviced to patients with cancer since this approach increases glucosinolate contact with plant myrosinase and increases the amount of isothiocyanates and sulforaphane absorbed (Shapiro et al. 2001). Another important item to concern carefully to increase the anticancer potential of glucosinolates and sulforaphane is the necessity of steaming or microwaving in food preparations for the patients with cancer since these compounds are water-soluble and thus may decrease 18-59 % after boiling cruciferous vegetables for 9-15 minutes (McNaughton and Marks 2003) and myrosinase can be inactivated because of the boiling at high temperatures (Conaway et al. 2000; Rouzaud et al. 2004).

The formation of DNA adducts is recognized as the initial step

in the chemistry of carcinogenesis and thus blocking the formation of the DNA adducts may be a crucial first step in cancer protection. Glutathione-S-transferases inactivate carcinogenes, converting them into less toxic and inactive metabolites through reduction of the formation of the DNA adducts. One of the important reasons for the very high incidence of cancer may be the poor or lack of GST Mu, one of the glutathione S-transferases which are the isozymes that can regulate mitogen-activated protein kinases or can facilitate the addition of glutathione to cysteine residues in target proteins (McIlwain et al. 2006), and persons possessing this genotype are predisposed to a number of cancers including breast, cancer, prostate, liver and colon cancers (Sheweita and Tilmisany 2003). Sulforaphane is thought to protect GSTM1 from mutation and formation of its DNA adducts which may be the reason for the lower incidence of various types of cancer, especially in GSTM-positive subjects who consumes more sulforaphane rich foods such as broccoli (Gasper et al. 2005).

An important amount of data claim a close link between sulforaphane and phase II enzymes which abrogate oxidative stress by scavenging the reactive oxygen species after their conversion from fat into water soluble form. Confirming this, the oral administration of broccoli sprout as 200 g/d for three successive days increased the RNA expression of sentinel phase II enzymes (Riedl et al. 2009). The induction of phase 2 enzymes by sulforaphane has been confirmed for various cancers including prostate cancer cells (LNCaP, MDA PCA 2a, MDA PCa2b, PC-3 and TSU-Pr1) (Singh et al. 2004; Brooks et al. 2001), human colon cancer cells (HT29) (Parnaud et al. 2004), lymphoblastic leukemia cells (LCL) (Suppipat et al. 2012), skin cancer cells (Dinkova-Kostova et al. 2007). On the other hand, Oltipraz (Miao et al. 2003), Zerumbone (a tropical ginger sesquiterpene) (Nakamura et al. 2004) and 6-DG (6 dehydrogingerdione, one of the major components of ginger, *Zingeber officinale*) (Yao et al. 2014) using treatments may benefit from sulforaphane and sulforaphane rich foods since all of them induce phase II activity. The most important point which should be taken into consideration in cancer nutrition in the part of the induction of phase II enzymes by sulforaphane and the mentioned drugs is Zeaxanthin (Zea). The carotenoid pigment in human retina and some foods; egg

yolk, maize (corn), red seedless grape, zucchini squash, orange pepper, cucumber, green pepper, orange juice, honeydew, celery, green grapes, Brussel sprouts, orange, mango, tomato juice and peach (Sommerburg et al. 1998) may enhance the anticancer effect of ginger (which contains 6-DG), Oltipraz and Zerumbone, and the sulforaphane rich foods; white cabbage, broccoli, red cabbage, cauliflower, Brussels sprouts, radish, mustard, turnip and Chinese kale (Totusek et al. 2011; Farag and Motaal 2010) since both the pigment, sulforaphane and the mentioned drugs induce the activity of phase II enzymes.

Phytoene, a 40 carbon intermediate in the biosynthesis of carotenoids, having a maximum UV visible absorption, ranged at 286 nm, is another strong carotene antioxidant with its rich sources; apricot, banana, carrot, cherry, grapefruit, melon, orange, pepper (red or orange), tomato and watermelon (Biehler et al. 2011). The other group of carotenoids besides carotenes is xanthophylls which include the yellow leaf pigments with a similar structure to carotenes, but they contain oxygen atoms while carotenes are purely hydrocarbons with no oxygen. They are found in the leaves of green plants in high quantities, modulate light energy, serving a non-photochemical quenching agent at high light levels in photosynthesis. Lutein rich sources are; greenleafy vegetables, such as spinach or kale (Sommerburg et al. 1998; Abdel-Aal et al. 2013; Aman et al. 2005 and Azevedo and Rodriguez-Amaya 2005), zeaxanthin with its rich sources; paprika (Rutkowska and Stolyhwo 2009), egg, artichoke, asparagus, broccoli, Brussel sprouts, cilantro (a kind of coriander which is also known as Chinese parsley), cucumber, endive, lettuce, parsley, pepper (green or orange), scallion, spinach, tomato and zucchini (Perry et al. 2009). Cryptoxanthin, a provitamin A carotenoid with its richest sources; oranges, orange juice and other citrus fruits (Granado et al. 1996), pumpkins, persimmons, leafy vegetables and some animal products such as egg yolk and butter (Wu et al. 2013), canthaxanthin with its rich sources; green algae, crustaceans and fish (Palozza and Krinsky 1992), astaxanthin, yellow plant pigments from xanthophylls family of carotenoids with its rich sources; crustaceans (Becerra et al. 2014) and rubixanthin, a natural xanthophylls pigment with a red-orange color in rose hips (Anderson et al. 2011) are the other important phytochemicals in vitamin A origin.

Terpenes and terpenoids (which are also mentioned in detail in its related part), are a class of phytochemicals, many of which are aromatic hydrocarbons. The additional functional group to hydrocarbon structure is the initial difference between terpenes and terpenoids. Both terpenes and terpenoids are the primary constituents of the essential oils of plants and flowers. Monoterpenes, the most known functional terpenes with isoprene units, are limonene with its richest sources; the peels of citrus fruits (Matura et al. 2002), cherry (Xu et al. 2007), spearmint (Bertea et al. 2003), dill (Huopalahti and Linko 1983), celery (Sowbhagya et al. 2010), ginger (Jiang et al. 2006) and basil (Filip et al. 2014). Other important phytochemicals are; perillyl alcohol, the cyclic monoterpene and a hydroxylated derivative of d-limonene, with its rich sources; cherry (Serra et al. 2010), mint, citrus fruits and cranberries (Lee et al. 2001). Another group of phytochemicals, triterpenoids, are the metabolites of isopentenyl pyrophosphate oligomers with a backbone of 30 carbon isoprenoid molecule and isoprene units (Patlolla and Rao 2012). One group with its most common and widest use in both medicine and clinic nutrition as in drug form is saponins. They are the chemicals both hydrophilic (water-loving) and lipohilic (fat-loving) properties. Its rich sources are namely; alfalfa (Wina et al. 2005), soybean (Kim et al. 2004), legume (Shi et al. 2004) and maize (Okechukwu et al. 2013).

Betains, the phytochemicals which are the yellow indole-derived pigments of the plants, caryophyllales (the flowerin plants namely cacti, carnations, amaranths, beets) have got strong antioxidant potential since they are degraded first when subjected to light, heat and oxygen. Hence, they are used in frozen products and the food products with short shelf life. The well-known betalains are bitamin with their rich source are; beetroot (Gonçalves et al. 2012), indicaxanthin with its richest source, the fruit, *Opuntia ficus-indica* (Guesmi et al. 2013), vulgaxanthin with its richest source, berry cactus fruit (Correa-Betanzo et al. 2011). Chlorophyll, the other phytochemical, is the green pigment which exists in the chloroplasts of algae and plants, is as an extremely important biomolecule, not only as critical in photosynthesis, but also as antioxidant and anticancerogen while its rich sources are; spinach, parsley, dill and kale (Arnold et al. 2014).

Another group of phytochemicals is organic acids, namely phytic

acid or phytate, a saturated cyclic acid, with its rich sources; brans, seeds, grains, nuts and legumes (Steadman et al. 2001; Coulibaly et al. 2011). The organic acid is not digestible to humans and nonruminant animals, but more important point about it is that it inhibits the absoroption of certain important minerals and vitamins such as; zinc, iron, calcium and magnesium (Hallberg et al. 1987; Bohn et al. 2004; Lopez et al. 2002). Opposite to the inhibitory effect of phytic acid on mineral absorption, vitamins namely ascorbic acid prevents the inhibitory effect of phytic acid (Siegenberg et al. 1991; Soares et al. 2004). The inhibitory effect of phytic acid on mineral absorption makes it one of the most important determiners for the anticancerogenic or cancerogenic potential of the food since many of the minerals which are inhibited by the organic acid such as Ca, Zn, Se and Mg have significantly important anticancerogenic effects. The food processing and preservation practices like thermal processing, mechanical processing (household pounding to remove the bran and/or germ from cereals), soaking of cereal and legume and fermentation prevent the inhibitory effect of phytic acid on mineral absorption (Hotz and Gibson 2007). All these processes, by removing or hydrolyzing the organic acid, may contribute to the anticancer effect of these minerals. But, this approach is only from the side of phytic acid's inhibitory effect. For example, thermal processing can enhance the bioavailability of thiamin, vitamin B_6, niacin, folate and carotenoids by releasing them into plant matrix (Yeum and Russell 2002), but may cause losses in activity of heat-labile and water soluble vitamins (e.g. thiamin, riboflavin, vitamin C and folate). Shortening the cooking times and using the steaming process instead boiling, may decrease such losses in the mentioned vitamins. Briefly, the mentioned food processing and preparation practices as combined with shorter cooking times and steaming may increase or protect the anticancer potential of especially cereals and legumes, lowering their phytic acid content.

Lupane-type triterpenoids namely lupeol, betulin and betulinic acid are naturally exist worldwide in many vegetables, fruits and plant species. The richest sources of lupeol are olive, mango, fig and strawberry (Chaturvedi et al. 2008). Betulin, the other lupine, is exist with the richest amounts, in outer barks of white birch *Betula papyrifera Marsh.*(paper birch) which grows in the northern boreal

forest of Canada (Krasutsky 2006). Betulinic acid richest source, like in betulin, is the birch tree (Galgon et al. 1999 and Cole et al. 1991). Betulinines are soluble in chlorinated solvents (e. g. chloroform) or other ethers (e. g. THF, dioxane), but poorly soluble in water and water-based solvents because of their lipophilic and rigid carbon skeleton (Sarek et al. 2003). This indicates to the higher bioavailability and stronger anticancerogenic effect of the compounds in fatty plant origin foods but also reveals a question of the foods having higher fat and fructose contents which are cancerogenic. Should such foods be evaluated as cancerogenic or cancer promoting with their higher fat and fructose contents or rather anticancerogenic because of their rich betulin contents?. For example, betulinie and other lupine rich foods namely strawberry, mango, olive and fig, especially the two; mango and olive, are very high in fructose and fat as compared with many other plant origin foods but also the two richest ones in lupine saponins. Betulin was shown to have anticancer effect which results in apoptosis (cervical cancer), HepG2(liver hepatocellular), A549 (lung adenocarcinoma) and MCF-7 (breast cancer) cell lines by depolarizing of mitochondrial membrane, releasing of the mitochondrial cytochrome c (the main component for the electron transport in mitochondria) and activating caspase-9 and caspase-31-7 (the enzymes, proteases, which proteolyse and hence decompose the proteins in mitochondrial membranes when activated) (Li et al. 2010). Betulin (25-50 mg) was determined to have anticancer effect on MDA-MB-231, MCF-7 and HS578T human breast cancer cell lines (Serafim et al. 2014).) Similarly, the leaves of coffea (Jager et al. 2009) which are rich in ursolic acid with its anticancerogen effect, are also a group of triterpene saponins like lupine and high in fat and fructose. Betulinic acid and betulin (20 mM) were claimed to cause apoptosis on 518A2 (human melanoma), A549 (lung cancer), FaDu (head and neck cancer), HT-29 (colon cancer), MCF-7 (breast cancer) and WWO70327 (human fibroblasts) cell lines (Kommera et al. 2009). Lupane-type triterpenoids derived from the leaves of *Heteropanax fragrans* as in 10-5 mol/L causes apoptosis on KB (Keratin forming-papilloma tumor) cell line (Zhao et al. 2011). >100 μM lupeportlandol, a new lupine triterpene derived from *Euphorbia portlandica*, shows anticancer activity on MCF-7 (breast cancer), NCI-H460 (non small

cell lung cancer) and SF-268 (Central nervous system lymphoma) cell lines (Madureira et al. 2004). Another and new lupine-type triterpene, ochraceolide (>20.0 μg/mL) on BC1 (breast cancer), HT (fibrosarcoma), LU1 (lung cancer), Mel2 (melanoma), Col2 (colon), KB (oral epidermoid, A-431 (epidermoid carcinoma), LNCaP (prostate), U373 (glioma) and ZR-75-1 (hormone-dependent breast cancer) cell lines (Sturm et al. 1996). Finally, glceryl esters of betulin and betulinic acid were shown to have anticancer effect on A549 (lung cancer), DLD-1 (colorectal adenocarcinoma) and WSI (skin fibroblast) cell lines (Thibeault et al. 2012).

The vitamin A rich foods; chard, cilantro, collards, corn, cabbage, carrot, Brusses sprouts, broccoli, green beas, asparagus, apple, banana, pear, avocado, grape leave, lettuce, mango, melon, okra, onion, orange, red pepper, Japanese persimmons, raspberries, winter squash and tomato (Holden et al. 1999), the vitamin C rich foods; red pepper, orange, green pepper, broccoli, tomato, cantaloupe, cabbage, cauliflower, potato, spinach, greenpeas (USDA1 2001) and vitamin E rich foods; cauliflower, potato, leek, onion, parsley, cucumber, cod fish, cottage cheese and coconut (Sundl et al. 2007) may be in a stronger anti-cancer effect via the phase II enzymes and Keap/Nrf2/ARE, if the mentioned vitamins A, C and E rich foods are combined with sulforaphane rich foods mentioned above, especially during the treatments with 6-DG, Oltipraz and Zerumbone since all the mentioned foods and drugs induce the expression of phase II.

Keap 1 (Kelch EcH associating protin 1) is a protein that binds Nrf2 and promotes its degradation by the ubiquitin proteasome pathway. In Nrf2-Keap 1 signaling pathway, two Keap molecules bind to Nrf2 to polyubiquitylate it which results in rapid Nrf2 degradation by the proteasome. A small proportion of Nrf2 escapes from the inhibition and accumulates in the nucleus to mediate basal Antioxidant Response Element (ARE) gene expression, which results in cellular homeostasis. But if the binding of Keap 1 with another protein Cul3 (the member of the cullin protein family which plays a critical role in the polyubiquitination and subsequent degradation of specific protein substartes like Nrf2) is distrupted in response to electrophiles, this disruption leads to the escape of Nrf2 (Kansanen et al. 2013). At this point, sulforaphane modifies

multiple Keap 1 domains whereas electrophiles like dexamethasone mesylate and biotinylated iodoacetic acid modify Keap 1 preferentially in the central linker domain (Dinkova-Kostova et al. 2002). The other Nrf2 activators besides sulforaphane as the naturally occurring, plant-derived phytochemicals are; curcumin, epigallocatechin-3-gallate, resveratrol, cafestol-also exist in decaffein added coffee which may be crucial in cancer nutrition (Trinh et al. 2010), kahweol, cinnamonyl-based compounds, zerumbone, garlic organosulfur compounds, lycopene and carnosol (Martin et al. 2004; Ungvari et al. 2010; Hwang and Jeong 2008; Na et al. 2004; Dai et al. 2014; Shin et al. 2011; Wondrak et al. 2010 and Padiya et al. 2014). NAD(P)H: quinine reductase (NQO1), glutathione S-transferase (GST), ϒ-glutamylcysteine synthetase, uridine diphosphate glucuronosyl transferases and epoxide hydrolase are the genes that induce Nrf2 activation. On the other hand, Rutaecarpine, a quinazolinocarboline alkaloid isolated from *Evodia rutaecarpa* (Juss.) can activate one of these genes, NQO1 and induces Nrf2 activation (Ahn et al. 2008). Besides sulforaphane and the mentioned food substances, also D-Limonen (1-methyl-4-isopropyl-cyclohexene), a natural product in the essential oils of orange, lemon, mandarin, lime and grapefruit, induces Nrf2 activation via the glutathione S-transferase (GST) (Chaudhary et al. 2012). Oltipraz, an organosulfur in cruciferous vegetables like Brussels sprouts and cabbage (Benson 1993), phenethylisothiocyanate (PEITC) in *Brassicaceae* family vegetables such as cabbage, cauliflower, watercress and broccoli (Fenwick et al. 1983), α-tocopherol and α-tocopherol rich foods; cauliflower, potato, leek, onion, parsley, cucumber, codfish, cottage, cheese and coconut (Sundl et al. 2007), coumarin and coumarin rich foods; green plants, billbery, cloudberry, greentea (Bubols et al. 2013), indol-3-carbinol(I3C) and I3C rich foods; Brussels sprouts, cabbage, cauliflower, collordgreens, kale, Kohlrabi, mustard, rutabaga, turnips, bok choy, Chinese cabbage (Kristal and Lampe 2002), β-carotene rich foods; chard, cilantro, collards, corn, cabbage, carrot, Brussel sprouts, broccoli, green beas, asparagus, apple, banana, pear avocado, grape leave, lettuce, mango, melon, okra, onion, orange, red pepper, Japanese persimmon, raspberries, winter squash and tomato (Holden et al. 1999), are the nutrient substances and antioxidants which induce the activation of glutathione S-transferase

(GSI) and thus activate Nrf2. Therefore, the combined nutrition of all the mentioned foods may be beneficial in cancer nutrition during anti-cancer treatments. Since some of the mentioned foods are rich in sulforaphane like Brussels sprouts and broccoli (Farag and Motaal 2010) and sulforaphane induce Nrf2 activation via quinine reductase, the mentioned combined nutrition may also be useful in cancer nutrition, inducing Nrf2 activation.

Biologically active isothiocyanates (ITCs) and sulforaphane which is derived from glucoraphanin from its richest sources; broccoli, Brussels sprouts, cauliflower and cabbage have an extraordinary ability to induce expression both phase II and antioxidant enzymes such as vitamin A, C and E via the Keap/Nrf2/ARE (Boddupalli et al. 2012). Furthermore, sulforaphane is amongst the most potent naturally occurring inducers of Nrf2 signaling. Sulforaphane is an electrophile that can react with protein thiols to form thionoacyl adducts. Prior to the modification of Keap 1 which results in the escape and activation of anticancerogen and antioxidant Nrf2, thiols react with sulforaphane by adding carbon to the isothiocyanate to yield thionoacyl adducts. The sulforaphane thionoacyl adducts modify Keap 1, most readily in the Kelch domain which is the most sensitive part of Keap 1 to thiol (Hong et al. 2005). The followed distruction of Keap 1 leads to escape of Nrf2, inducing its anticancerogen and antioxidant effect. Briefly, sulforaphane is an electrophile, which shows its protective effect against various cancers via the Keap/Nrf2, activating and inducing Nrf2.

The same interesting point as related to the 'anticancerogenic effect and ROS' association also appears for sulforaphane. Sulforaphane was informed to decrease the cell growth of human bronchial epithelial BEAS-2B cells after the generation of ROS at a high rate while the pretreatment with antioxidant N-acetylcyteine (NAC) blocked sulforaphane induced decrease in cell growth. Erk1/2, the protein-serine/threonine kinases whose activation generally promotes cell curvival, but under certain conditions, (Lu and Xu 2006), apoptosis was activated after the addition of sulforaphane (Lee and Lee 2011). These findings not only indicate to the antiprolific effect of sulphoraphane due to its Erk1/2 activation (which was also confirmed by Keum et al. 2006; Jo et al. 2014; Yeh and Yen 2005 and Li et al. 2014) and ROS

generation which is a critical point in cancer nutrition, but also they introduce the very thin border between an antioxidant and oxidant. Under the highlight of these findings and many others which claim the ROS generation induced by antioxidants (Sam et al. 2005; Regensburger et al. 2012; Carr and Frei 1999; Bland 1998), we have currently come to a point that both an antioxidant and oxidant produce ROS and if they are evaluated by considering to their association with ROS, both are oxidants. But, an antioxidant seems to have other important antioxidant effects like inducing Nrf2 or activation of Erk 1/2 which reveals its overall antioxidant potential while it may induce the generation of ROS. Sulforaphane generates ROS but induces apoptosis on cancer cells like many other anticancerogenic and antioxidant substances by using these ROS. The substance also induce the antiprolific and anticancerogenic effect by scavenging superoxide or inducing the activations of Nrf2 and Erk1/2 (Mates et al. 2000) which are not exist in an oxidant. The mentioned differences in the functional status of antioxidants should have been taken into consideration immediately in cancer nutrition and clinic nutrition since the antioxidants like vitamin C or sulforaphane which have already been informed as oxidants in public media of many countries including many developed countries like United States and European countries by only considering their relation with ROS generation while disregarding many of their other antioxidant and anticancerogenic effects, especially killing tumor cells by using ROS which they regenerate. Currently, it is well documented that, sulforaphane, though it is an antioxidant, generates ROS which leads to apoptosis in various cancers like leukemia, bladder cancer, prostate cancer, breast cancer, osteocarcinoma, urinary bladder cancer, neuroblastoma and glioma (Choi et al. 2008; Amin and Shankar 2015; Park et al. 2014; Singh et al. 2005; dr Oliveira et al. 2014; Jo et al. 2014; Tarozzi et al. 2009 and Jiang et al. 2010). Because of the mentioned tumor killing potential of sulforaphane by using ROS, the drugs which induce apoptosis by using ROS, mentioned in resveratrol; sunitinib, sorafenib, tetrandrine, cisplatin, 17AAG, DBeQ, ritonavir and brefeldin A may show a greater anticancer and apoptotic effect if administered as combined with sulforaphane and sulforaphane rich foods (like white cabbage, broccoli, red cabbage, cauliflower, Brussels sprouts, radish,

mustard, turnip and Chinese kale) since both of the mentioned dugs and sulforaphane induce apoptgosis by increasing ROS.

Because of the activation or the enhancement of ERK1/2 phosphorylation by PD98059 (2-amino-3-methoxyflavone) (Cerioni et al. 2003, Gefitinib (Favoni et al. 2010), Cisplatin (Gozdz et al. 2008), Sorafenib (Spirli et al. 2012), Paclitaxel (Okano and Rustgi 2001), Brefeldin (Dong et al. 2013), Octahedral pt(IV) complex K101 (Kwon and kim 2006), Thapsigargin (Arai et al. 2004), Bartezomib (Kao et al. 2014), Metformin (Rice et al. 2009), Raloxifene (Hisamoto et al. 2001) and 12-O-tetradecanoyl-pharbol-13-acetate (TPA), thapsigargin combination (Rodland et al. 1996) and valproic acid (Michaelis et al. 2006), should be administered as combined with sulforaphane or sulforaphane rich foods like white cabbage, broccoli, red cabbage, cauliflower, Brussels sprouts, radish, mustard, turnip and Chinese kale since both these drugs and sulforaphane activate Erk 1/2 and thus the synergism may much more increase the anticancer effect of the mentoned drugs, increasing ROS that target tumor. But, the drugs which inhibit Erk 1/2; sunitinib (Fenton 2010), vorinostat (Dasmahapatra et al. 2007), ritonavir (Adler-Wails et al. 2005), radicicol (Youn et al. 2013), vorinostat (Akada et al. 2012), tamoxifen (Wang et al. 2013; Tian et al. 2009), Geldanamycin (Setalo et al. 2002), lapatinib, fulvestrant (Emde et al. 2007), PD98059 (Chandrasekar et al. 2000), UO126 (Choi et al. 2013), Honokiol (Zhu et al. 2011), SNX2112 (Friedman et al. 2013) administrations may not be advised as combined with sulforaphane and sulforaphane rich foods because sulforaphane and sulforaphane rich foods may stimulate Erk 1/2 activity and hence may decrease the effect of the mentioned drugs.

The acetylation of histones which are highly alkaline proteins, is important in gene regulation while specific modifications in the acetylation pattern of histones appear as one of the most common pathological changes in cancer. Thus, the use of histon deacetylase inhibitors has become a novel strategy in cancer chemoprevention. Sulforaphane has appeared a novel chemoprevention agent by inhibiting histon deasetylase activity, similar to the other histon deactylase inhibitor drugs, used in cancer chemoprevention (Ho et al. 2009). The mentioned ability of sulforaphane to target the aberrant acetylated

histones while activating the anticancer and detox phase 2 enzymes may be concerned to have a crucial role in cancer chemoprevention. Histone deactylases and histone acetylases, the enzymes that are responsible for deactylating and acetylating histons are the main causes in chromatin changes which regulate transcription and may regulate other nuclear events. The aberrant recruitments of histon deactylases and histon acetylases have shown to have important role especially in acute myeloid leukaemias. The anticancer effects of the most commonly administered histon deactylase inhibitors namely; AN-9 (in lung cancer melanoma and leukaemias), sodium phenylbutyrate (in leukaemias and myelodysplasia), valproic acid (leukaemias, myelodysplasia and cervical cancer), FK-228 (in T-cell cutaneous or peripheral lymphoma, MS-275 (in refractory solid tumours), suberoylanilide hydroxamic acid (in refractory solid tumours), LAQ-824 (in refractory solid tumours) and PXD101 (in advanced solid tumours) (Minucci and Pelicci 2006) may be enhanced if the administration of each of the mentioned histon deactylase inhibitors is combined with sulforaphane or sulforaphane rich food consumption (like cruciferous vegetables) which should be concerned in the current status of cancer nutrition.

COX enzymes including COX-2 play a key role in synthesizing prostaglandins from arachidonic acid that is released from the plasma membrane by the action of phospholipase A2. The prostaglandin PGE2 and its precursor PGH2 produced by the cyclooxygenase acyivity of COX induce inflammation and cell proliferation. Sulforaphane was informed to have suppressed the expression of microsomal prostaglandin E synthase (mPGES-1), the enzyme that directly synthesizes PGE2 in sulforaphane mediated mPGES-1 suppression. Sulforaphane suppresses the expression of Hypoxial Inducible Factor 1 alpha, HIF-1 α, a protein that binds specific DNA sequences and responds to changes in available oxygen in the cellular environment and decreases in oxygen, leading to hypoxia (Smith et al. 2008). Additionally, the presence of HIF-1α reduces the transcription of mPGES-1 (Zhou et al. 2012).

Another anticancer effect of sulforaphane by inhibiting COX-2 which induces proliferation appears to form via nuclear translocation of NF-kappaß, the protein whose incorrect regulation has been linked to cancer. The binding of NF-kappaß to COX-2 results in activation

of COX-2. Sulforaphane induces nuclear translocation of the protein and reduces its binding to COX-2 gene promoter, a key mechanism for suppressing COX-2 expression by sulforaphane (Shan et al. 2009). Sunitinib's anticancer effect and apoptotic potential may become greater in case of COX-2 inhibition by sulforaphane (Wang et al. 2013; Morais 2014 and Sanchez et al. 2013) which directly indicates to the importance and necessity of the combination of 'sunitinib and sulforaphane and sulforaphane rich foods' since sulforaphane enhances the anti-cancer effect of sunitinib by inhibiting COX-2. Similarly, the drugs that inhibit COX-2; celecoxib, sorafenib (Cervello et al. 2013), radicicol (Chanmugam et al. 1995), metformin (Kim and Choi 2012), magholol, honokiol, eugenol, bis-eugenol (Murakami et al. 2012), tetrandrine (Wu and Ng 2007), 17 AAG (Katiyar 2015), raloxifen (Zeng et al. 2005), rafecoxib (Bombardier et al. 2000), Naproxen (Dhir et al. 2006), dexamethasone, hydrocortisone, triamcinolone, acetonide, methyl prednisolone, beclomethasone, diproprionate (Croxtall et al. 2002) and nafoxidine (Lednicer 2002) may show greater apoptotic effect if used as combined with sulforaphane and sulforaphane rich foods since sulforaphane also inhibits COX-2 like the mentioned drugs.

On the other hand, the drugs that induce the expression of COX-2; vorinostat, trichostatin A (Wang et al. 2013), thapsigargin, okadaic acid, calcium ionophore A23187 (Ledwith et al. 1997), brefeldin A, tunicamycin (Hung et al. 2004), fulvestrant (Cuzzocrea et al. 2006), R(+)-methanandamide, anandamide, tetrahydrocannabiol (Rosch et al. 2005), 12-O-tetradecanoylphorbol-13-acetate (TPA) (Zhang et al. 2008), versipelostatin (Nakamura et al. 2007), lactacystin (Chen et al. 2005), MG-132 (Singh et al. 2012), may show less inflammatory effect as one of their side effects when they are administered as combined with sulforaphane supplements or sulforaphane rich foods which inhibits COX-2 activity and expression (Shan et al. 2009; Woo and Kwon 2007; Kim et al. 2014; Lin et al. 2008 and Cho et al. 2009), during cancer treatments.

P38, are mitogen-activated protein kinases which are responsive to stress stimuli such as cytokines, ultraviolet irradiation and heat shock. Sulforaphane modifies p38 in MCF-7 human breast cancer cells, treated with 12-O-tetradecanoylphorbol-13-acetate (TPA), a chemical

to induce carcinogenesis, and prevented TPA-reduced phosphorylation of p38 while activating caspase-7 associated with apoptosis in MCF-7 cells (Jo et al. 2007). P38 is activated upon cellular stress and often engages pathways that can promote apoptosis (Bulavin and Fornace 2004), because it can inhibit cell growth by decreasing the expression of cyclin D (Lavoie et al. 1996) which is a protein to regulate cell cycle progression.

Apopptotic cell death and regulated expression of apoptosis involve genes, proteases, protein kinases, phosphatases, endonucleases, all of which cause the cell dismantling and the formation of apoptotic bodies. The key components of this self-distructing machinery are the caspases, which are the proteases, consisted of two groups; the initiators and the effectors. The initiator caspases (-2, -8, -9, -10 and -11) activate the second group of caspases (-3, -6 and -7). The second group, effectors, can degrade proteins in the cell nucleus and cytoplasm which results in the deregulation of vital cell processes and ultimately apoptosis (Philchenkov et al. 2004). Caspases, a group of proteins that mediate apoptosis, are divided into two groups as the group 1; the inflammatory caspases that are involved in cytokine maturation and group 2; which regulate apoptosis, subdivided into two classes as initiator caspases (caspase-2, -8, -9 and -10) and effector caspases (caspase -3, -6 and 7). Effector caspases target a broad spectrum of cellular proteins, leading to cell death while initiator caspases are to be translated as monomeric zymogens (enzyme precursors). The two main apoptosis pathways are; the extrinsic receptor mediated and the intrinsic mitochondrial pathways. In extrinsic receptor-mediated apoptosis, extracellular ligands stimulate receptor oligomerizatioin and the death-inducing signaling complex (DISC) assembly, and in the extrinsic receptor-mediated apoptosis, proteins from the BcL-2 family control mitochondrial integrity while, caspase-3, -6, -7 and 8 induce the distruption of mitochondrial integrity and subsequently apoptosis (Olsson and Zhivotovsky 2011). Sulforaphane, as combined with a specific Bcl-2 inhibitor, HA14-1, induces apoptosis by activating caspase-3 in human leukemia 4937 cells (Jin et al. 2007). The activation of effector caspases is not only caused by initiator caspases but also non-caspase proteases, such as; cathepsins, calpains and granzymes, the serine proteases that are released by

cytoplasmic granules within cytotoxic T cells (a T lymphocyte, a type of white blood cell that kills cancer cells) and natural killer (NK) cells (the cytotoxic lymphocytes which are critical to the innate immune system by giving immediate responses to viral infections and cancerous formations) (Johnson 2000). The apoptotic effect of sulforaphane via the induction of caspase enzymes have also been confirmed by Singh et al. 2004; Pledgie-Tracy et al. 2007; Park et al. 2007; Suppipat et al. 2012; Chen et al. 2012; Huang et al. 2012, in prostate, breast, liver, lymphoblastic leukemia, colorectal and brain malignant glioma. Sunitinib (Yang et al. 2010), sorafenib (Huang et al. 2010), reolysin (Carew et al. 2012), toyocamycin, sangivamycin (Kim et al. 2005), tetrandrine (Yu et al. 2014), bortezomib (Zhao et al. 2008), paclitaxel (Mielgo et al. 2009), brefeldin A, sanguinarine (Larsson et al. 2010), parthenolide, geldanamycin (Lee et al. 2012), radicicol (Kim et al. 2012), the gene therapies; Apaf1, FADD, Smac/DIABLO (Cain etal. 2002), retaspimycin (IPI-504, SNX-2112 (Davenport et al. 2007), daunorubicin, doxorubicin, etoposide, mitomycin c (Wesselborg et al. 1999), cisplatin, dactinomycin (Tao et al. 2007), honokiol (Park et al. 2005) and MG-132 (Yuan et al. 2008), all of which induce caspase activity amy show better anticancer potential if administered as combined with sulforaphane and sulforaphane rich foods since sulforaphane and sulforaphane rich foods induce caspase activity. The sulforaphane and caspase inducer combined application may enhance the anticancer potential of the drugs by activating caspase-activated DNAse(CAD) and releasing the cytochrome c efflux more. The activation of effector caspases is not only caused by initiator caspases but also non-caspase proteases, such as; cathepsins, calpains and granzymes, the serine proteases that are released by cytoplasmic granules within cytotoxic T cells (a T lymphocyte, a type of white blood cell that kills cancer cells) and natural killer (NK) cells (the cytotoxic lymphocytes which are critical to the innate immune system by giving immediate responses to viral infections and cancerous formations) (Johnson 2000).

Cisplatin, transplatin (IV) chloride, anisomycin (Shan t al. 2010; Losa et al. 2003), brefeldin A, thapsigargin, tunicamycin (Kim et al. 2010), tamoxifen (Gutierrez et al. 2005), betulinic acid (Godugu et al. 2014), honokiol (Lee et al. 2006), bortezomib (Lioni et al. 2008),

4-phenyl-3-butenoic acid (PBA) (Matesic et al. 2012), vorinostat (Sun et al. 1011, geldanamycin (Lingelem et al. 2015), raloxifen (Mori-Abe et al. 2003), paclitaxel (Reshlin et al. 2003) and panaxydol (the roots of Panax ginseng) (Kim et al. 2011) may better be administered without sulforaphane or sulforaphane rich foods since sulforaphane down-regulates p38 activity (Rudolf et al. 2014; Jo etal. 2007; Eun-Hye et al. 2007; Chen et al. 2009 and Nguyen et al. 2014) and thus, may block the mentioned drugs to decrease the expression of cyclin D which may cause them to show less anticancer effect.

Various inducers of apoptosis directly or indirectly influence the permeability of the outer mitochondrial membrane and cause to the release of cytochrome c, a small hemeprotein which is found as loosely associated with the inner membrane of the mitochondrion, whose efflux is the key point in the activation of the mitochondria/apoptosome-dependent death pathway. On the other hand, caspase 3, caspase 7 and caspase 8 activate the cytosolic factor Cif (cytochrome c-efflux inducing factor) (Han et al. 1999). Another important indicator for the crucial role of caspases in apoptosis is the strong relation of caspase -6, -7, and -8, apoptosis inducing factor (AIF) (a flavoprotein) and cytochrome c, in which the efflux of cytochrome c activates caspase -6, -7, and -8, while translocating AIF from mitochondria to the nucleus during the process of apoptosis (Granville et al. 2001). Additionally, apoptotic internucleosomal DNA degradation is also regulated by caspase(s). Caspase-Activated DNase (CAD) is a protein codified by a gene with 338 nucleotides located in chromosome 1 and the protein breaks up the DNA which improves apoptosis. CAD is also activated by caspase 3 (Mukae et al. 1998).

Another effect of sulforaphane in cancer prevention is its block on phase 1 enzymes which chemically transform lipid soluble compounds into water soluble compounds which are more reactive than the original toxins and thus more destructive. Of the phase 1 enzymes, CYP1A1 is a protein and a member of the cytochrome P450 family of enzymes, encoded by CYP1A1 gene (Smith et al. 1998). The knockdown of CYP1A1 may also make a protection against cancer by markedly increasing the phosphorylation of AMP-activated protein kinase (AMPK), the enzyme as a central regulator of cellular metabolism and homeostasis whose

activation can cooperate with oncogenic drivers to reprogram tumor cell metabolism and enhance cell growth and proliferation (Faubert et al. 2015), decreasing phosphorylation and perturbation of AKT (serine/threonine-specific protein kinase) whose signals mediates signaling through cancer cells (Altomare and Testa 2005).

Hem oxygenase-1 (HO-1) is the intracellular enzyme which maintains cellular homeostasis under stress conditions. The enzyme degrades heme into carbon monoxide, biliverdin and ferrous iron as a response to any stress inducer and the biologically active products generated during the HO-1 mediated heme degradation play a significantly important role in the adaptation of cells to oxidative and cellular stresses. The response includes the inhibition of inflammation and the stimulation of cell proliferation (Banerjee et al. 2012). The association of (HO)-1 with malignancies and the resistance to chemo and radiotherapy have been claimed by Miyata et al. 2014; Lin et al. 2015; Miyake et al. 2010; Bai et al. 2013; Nielsen et al. 2014; Keshavan et al. 2004; Weinberg 1996; Hann et al. 1998; Marinissen et al. 2006. However, there are also studies which claim that HO-1 is apoptotic, anti-inflammatory and antiproliferative (Miyazaki et al. 2010; Ma et al. 2015; Paine et al. 2010; Alcaraz et al. 2003; Lin et al. 2008). In the second group of the studies which claim (HO)-1 as antiapoptotic and anti-inflammatory, carbon monoxide, free iron and biliverdin, produced by (HO)-1 have been regarded as an adaptive cellular response against inflammatory response and oxidative injury. But, as being in a complete conflict, the former group of the studies associates the same substances produced by (HO)-1 with the induction of proliferation and inflammation. Here, the crucial problem clearly seems that no matter how carbon monoxide, free iron and biliverdin, produced by (HO)-1 may be accepted as an adaptive cellular response againt inflammation and cancer, they are teratogen. In spite of the mentioned great conflict, by taking the risk of the teratogens, produced by (HO)-1 into consideration, the treatments which target (HO)-1 inhibition; tin (IV) protoporphyrin IX dichloride (SnPP), zinc (II) protoporphyrin IX (ZnPP) (Bussolati et al. 2004), zinc (II) deuteroporphyrin IX-2,4-bisethyleneglycol (Mayerhofer et al. 2004), imidazole-based compounds (8,9,10R,11,12,13,3 (Sorenti et al. 2012, caveolin-1(a protein and a tumor suppressor gene) (Taira et al.

2011), calcineurin (a protein phosphatase and calcium-dependent serine-threonine phosphotase) (Tongers et al. 2004), siRNA (a class of double-stranded RNA molecules, 20-25 base pairs in length), metformin (Do et al. 2013), Tin-mesoporphyrin (SnMP, a neuroprotectant that has also been used clinically to treat hyperbilirubinemia) (Wagner et al. 2000), ZnMP (zinc mesoporphrin) (Schuurmans et al. 2001), CrMP (crom mesoporphyrin) (Bundock et al. 1996), SnPP (tin-protoporphyrin IX) (Kaizu et al. 2003), ZnPP (Zinc protoporphyrin) (Wang et al. 2013), PEG-ZnPP (Pegylated zinc protoporphyrin) (Sahoo et al. 2002), OB-24 ([2-(4-bromophenyl)ethyl]-2-2[1H-imidazol-1-yl)methyl]-1,3-dioxolone hydrochloride) (Alaoui-Jamali et al. 2009), may be much more useful and reasonable since such treatments may lower the production rate of the mentioned teratogens; biliverdin, iron and carbon monoxide. But, capsaicin (CAP), dihydrocapsaicin (DHC, the major pungent components of hot peppers)(Kim and Lee 2014), enterolactone, a mammalian lignin and the plant lignans which can produce enterolactone such as secoisolariciresinol diglucoside, the richest sources; flaxseed, sunflower, sesame and pumpkin seeds (Strandas et al. 2008; Kivela et al. 2008), matairesinol (whole grains) (Niemeyer et al. 2003), lariciresinol (Brassica vegetables like Brussel sprouts and broccoli), pinoresinol (sesame and Brassica vegetables) (Milder et al. 2005), esculetin and coumarin (red clover, cinnamon)(Ballin and Sorensen 2014; Kim et al. 2014; Booth et al. 2006) and finally sulforaphane and sulforaphane rich foods; white cabbage, Brussel sprouts, radish, mustard, cauliflower, turnip and Chinese kale, arginine rich foods; turkey breast, beef, ground meat, lupin, soybean, nuts, seeds, egg white, peanut, mollusk, chickpea, soy flour, sesame seed, lentil, beans, chicken meat and porl meat and genipin (Gardenia fruit) (Totusek et al. 2011), the foods most of which also contain plant lignans that produce enterolactone (Lee and Lee 2011; Keum et al. 2006), should better be avoided during the treatments with these mentioned treatments and drugs since the indicated food substances and sulforaphane induce HO-1 and thus, may cause an inflammatory response, unlike the drugs.

Confirming this, both the increased levels of heme-oxygenase-1 and p21, the cyclin-dependenth kinase inhibitor which promotes cell cycle arrest in response to many stress stimuli, in gastric cancer cell lines,

MKN-45 and MKN-28, showed an obvious resistance to apoptosis (Liu et al. 2004).

The stimulation of angiogenesis, tumor growth and metastasis by HO-1 and its overexpression were also observed in pancreatic cancer cells, human adenocarcinoma cells and lung cancer cells (Sunamura et al. 2003; Nuhn et al. 2009; Kongpetch et al. 2012 and Lin et al. 2015).

In addition to sulporaphane, the other flavonoids; chrysin (which is found in the flowers of *Passiflora caerulea* and *Passiflora incarnate* (Wolfman et al. 1994; Brown et al. 2007), apigenin (in parsley, celery, celeriac and chamomile tea) (Nielsen et al. 1999; Miean and Mohamed 2001; Schreiber et al. 1990), luteolin (in *Terminalia chebula*, pollen and mint) (Bimakr et al. 2008; Saleem et al. 2002; Campos et al. 2002), baicalein (in the root of *Scutellaria baicalensis* and *Scutellaria radix* (Bonham et al. 2005; Ma et al. 2005), scutellarein (in *Scutellaria lateriflora* and *Asplenium belangeri*) (UmiKalsom et al. 1991), acacetin (in *Robinia pseudoacacia*, *Turnera diffusa*, *Betula pendula* and in the fern of *Asplenium normale* (Zhao et al. 2008; Valkama et al. 2004; Umikalsom et al. 1991), diosmetin (in Caucasian vetch (Andreeva et al. 1998), Eupatorin (in *Orthosiphon stamineus*) (Doleckova et al. 2012), Genkwanin (in *Alnus glutinosa*, *Notholaena bryopoda* and *Asplenium normale*) (Ciara et al. 2005; Umikalsom et al. 1991), kaempferol (in tea, broccoli, apples, strawberries and beans) (Somerset and Johannot 2008), quercetin (in onion, green pepper, cabbage, spinach, potatoe, buckwheat noodle, garland, chrysanthemum and Chinese cabbage, asparagus, tomato, broccoli, red leaf lettuce and green tea (Nishimuro et al. 2015) and myricetin (in broccoli, red chili, garlic, belimbi fruit, cashew, French bean, French pea, guava, kesom leaves, sesambu leaves, maman, kadok and black tea) (Miean and Mohamed 2001) inhibit phase 1 enzymes including CYP1A1 (Androutsopoulos et al. 2011). When the drugs which induce phase 1/CYP1A1 are considered, the drugs namely; sunitinib (Maayah et al. 2013), dasatinib, imatinib, nilotinib, sorafenib (Narjoz et al. 2014), SB203580 (Korashy et al. 2011), honokiol (Cho et al. 2014), bortezomib (Xu et al. 2012), aminoflavone, paclitaxel, camptothecin (Reinicke et al. 2010), tamoxifen, raloxifen (Williams-Brown et al. 2011), tunicamycin (Horikawa et al. 2006), tobacco (Roth et al. 2001), herbimycin A and geldanamycin (Perepechaeva et al. 2011) may

benefit from the use of sulforaphane supplements and/or sulforaphane rich foods and the other bio-active compounds and flavonoids may decrease the risk of water soluble toxins which are produced due to the induction of CYP1A1 by these anticancer drugs. On the other hand, the anticancer drugs/agents/bio-active compounds/flavonoids which inhibit CYP1A1, like; MG-132 (Anwar-Mohamed et al. 2008), metformin (Do et al. 2014), chalepensin (Ueng et al. 2013), ritonavir, efavirenz, rifampin, ketoconazole, dimethylsulfoxide 0.1% (Pillai et al. 2013), acacetin, polymethoxylated flavon eupatorin-5-methyl ether, diosmetin, eupatorin, di-hydroxylated flavones chrysin (Androutsopoulos et al. 2011), alpha-naphthoflavone, apigenin, isosafrole, fluvoxamine (Pastrakuljic et al. 1997), bergamottin (the grapefruit flavonoid) (Olguin-Reyes et al. 2012), caffeine (in coffee, tea, chocolate) (Eugster et al. 1993), pinostilbene, desoxyrhapontigenin, pterostilbene (Mikstacka et al. 2007), may yield much better prognosis if they are administered as combined with sulforaphane supplements and/or sulforaphane rich foods and the other bio-active compounds and flavonoids, creating a synergy via the inhibition of CYP1A1 and thus leading to a decrease in the level of water soluble toxic substances. The inhibitory effect of sulforaphane on CYPA enzyme system is also confirmed by Skupinska et al. (2009); Yang et al. (2013); Wiktorska et al. (2009); Elbarbry and Elrody (2011) and Gross-Steinmeyer et al. (2010).

B6, folate and Cancer

Folates and B_6 are very close vitamins in structure and function. This similarity is also exist in their anticarcinogenic effect that both vitamins maintain genomic stability by regulating DNA biosynthesis, repair and methylation, while deficiency of them induces and accelerates carcinogenesis by perturbing these processes (Duthie 2011).

Cancer begins to form with the change of DNA structure. One carbon atom from B_6 or folate utilizes the methylation of DNA in a healthy cell which means that carbon forms a methyl group and adds it into DNA structure. Either the insufficiency or excess of carbons which come from B_6 or folate may cause the improper methylation in DNA structure which is called as hypomethylation or hypermethylation (too many methyl group formations due to the high numbers of carbons coming from excess amounts of B_6 or folate). The excess carbon intake from B_6, folate or B_6 or folate rich foods may cause excess methylation in DNA structure which is called as hypermethyhlation. Cravo et al. (1994) observed the rectal mucosa from patients with carcinomas as significantly less methylated than in healthy controls. But, Roswall et al (2010) claimed the opposite that high dose folate supplementation could cause hypermethylation and cancer due to the hypermethylation. But, the high dose used in their study was 34 times more (325.3 microgram) than the median daily supplemental intake which is 100 microgram/day.

Another example for the polymorphisms which are caused by hypo or hypermethylation is often associated with regular and long term of alcohol consumption. Alcohol is one of the antagonists of folate and other methyl donors, e.g. methionine, an essential amino acid which is exist as in plenty amounts in animal origin foods like, meat, milk, meat and dairy foods, fish and marine origin foods, vitamins B_6 and B_{12} with B_6 and B_{12} rich foods). In the case, the MTHFR (methylentetrahydrofolate reductase) C677T enzyme polymorphism may form. The enzyme is critical in folate metabolism since it catalyzes the irreversible conversion of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate (which plays an important role in DNA synthesis). In case of the

MTFHRC677T polymorphism, 5,10-methyltetrafolate can not be converted into 5-methyltetrahydrofolate which results in the increase of 5,10-methylenetetrahydrofolate(homocyteine) (Kim 2003). 5,10 methylenetetrahydrofolate is essential for purine synthesis and 5,methylenetetrahydrofolate (homocyteine) is neccessary for methionine synthesis. The methionine or 5, methylenetetrahydofolate or 5,10 methyleneterahydrofolate increase as a result of folate or B_6 deficient nutrition causes extensive incorporation of uracil which is one of the nucleobases in DNA structure. DNA is consisted of nucleotides and nucleotides are consisted of nucleobases namely uracil, timin, adenin, guanin. 5,10 methyleneterahydrofolate supplies more methyl in case of its increase for uracil production which may result in an extensive incorporation of uracil into human DNA (4 million/cell). This extensive incorporation of the nucleobase, as a result of the imbalances in deoxynucleotide pools and DNA structure (Christman et al. 1993), may lead to chromosomal breaks in DNA structure which may be the likely cause of the increased colon cancer risk (Ames 2001). According to a great number of studies, like hypomethylation, the hypermethylation of certain genes may also break DNA sequence and initiate cancer growth. For this reason, the increase in folate and other carbon donors namely B_{12} and homocyteine in plasma may cause the hypermethylation of DNA which may result in cancer (Hultdin et al. 2005). Here, the most important parameter to take into consideration is the correct evaluation of such findings. Folate, B_{12} or B_6 may be cancer predisposing factors by causing hypermethylation in case of their high intakes for long periods, but the deficiencies may also increase the risk of cancer by causing hypomethlation of DNA in cell. The result clearly addresses a normal and healthy nutrition, should not only be in huge amounts, but also not in deficient amounts.

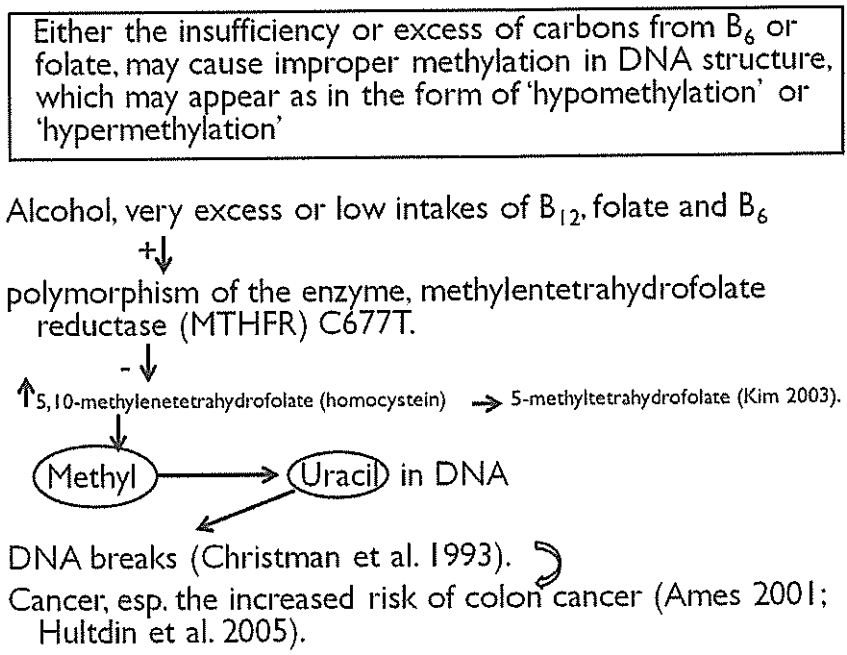


FIGURE 6

Another mechanism that explains the cancer increasing risk of folate deficiency is the increase of deoxyyuridine monophosphate/thymidylate (dUMP/dTMP) ratios besides the mentioned uracil misincorporation into DNA (Mashiyama et al. 2008). Deoxyuridine monophosphate is a nucleotide, a molecule that makes up the structural units of RNA (RiboNucleic Acid which is responsible for the protein synthesis) and DNA which controls and transfers genetic characteristics. Deoxyuridine monophosphate, like all other nucleotides, serves as chemical energy source as in the form of adenosine triphosphate. It also participates in cellular signaling (cyclic guanosine monophosphate and cyclic adenosine monophosphate) and is incorporated into enzymatic reactions as being a part of Coenzyme A and flavin adenine dinucleotide, the enzymes that play important role in energy production. Thymidylate enters into the structure of an enzyme, thymidylate synthetase, which is essential for regulating the normal DNA replication in healthy cells. The increase in deoxyuridine monophosphate and the decrease in thymidylate

concentrations due to B_6 vitamin deficiency means the increase and overload of energy in cancer cells which may enhance the degree of cancer invasion and the increase in enzymatic activity in cancer cells. Besides, the normal DNA replication and hence normal cell replication may be interupted due to the increase of thymidylate ratio due to B_6 deficiency. Now, an important question arises; Which one is correct?: The increasing effect on cancer risk of B_6 and folate rich foods because of the higher contents of fructose of B6/folate rich foods or, opposite, the increasing effect on cancer risk of B_6 deficient foods because of the energy increase in cancer cells as a result of the increase in the ratio of deoxyuridine monophosphate/thymidylate (dUMP/dTMP)!.

At the end of this part about folate/B_6 ana cancer below, are the cohort studies after 1990 which claim the anticarcinogenic or carcinogenic effect of folate and vitamin B_6. The studies were collected from Google and Sciencedirect databases. The anticarcinogenic effect of vitamin B_6 and folates in case of their regular and normal intakes, can be seen clearly. The reason of the selection of only cohort studies is that cohort studies requires the follow up of the patients and controls for long periods like weeks, months or years. Case studies only detect the effect for a very short period of time. Additionally, cohort studies use a much more massive data with a huge number of patients and control as compared with case studies. Therefore, cohort studies seem more reliable for evaluating an anticarcinogenic or carcinogenic effect of the food. While considering the cohort studies and their findings, another factor to take into consideration should be the status of B_6 which is not only its role in cancer. Vitamin B_6, also known as pyridoxine is a water soluble vitamin which helps to the formation of heme (the iron part of the red blood cells). Heme, the iron part of the red blood cells as combined with a protein component called as 'globulin' that forms hemoglobin carries oxygen inhaled. The transferred oxygen by the means of hemoglobin in red blood cells combusts glucose, the simplest sugar, in the cell, to produce energy (calorie). Briefly, energy is produced by oxygen and food in the cell and oxygen is carried by hemoglobin into the cell by hemoglobin in the red blood cells. Since B_6 plays an important role in the formation of heme in hemoglobin, oxygen can not be carried in enough concentrations into the other cells in case

of low production levels of hemoglobin due to the deficiency of the vitamin which may result in energy depletion. The vitamin also acts importantly in the production of relaxing hormon seratonin and thus the deficiency of the vitamin may lead to chronique fatique, stress, anxiety and depression. Another mechanism in the prevention against cancer with folate is formed by the means of the methylation of tumor supressor gene and DNA repair genes. High folate intake may cause methylation of unmethylated promoter sites of tumor suppressors and DNA repair genes like in the cases of adenocarcinomas and this, in turn, could be interpreted such that high folate intake induces a protection against to the progress of adenocarcinoma (Van den Donk et al. 2007). Long term ulcerative colitis may be a predisposed factor for the formation of colorectal cancers. Folic acid supplementation was shown to be inversely associated with longstanding ulcerative colitis (relative risks are 0.54 and 0.76 for 1.0 and 0.4 mg/d folate intakes respectively) (Lashner et al. 1997).

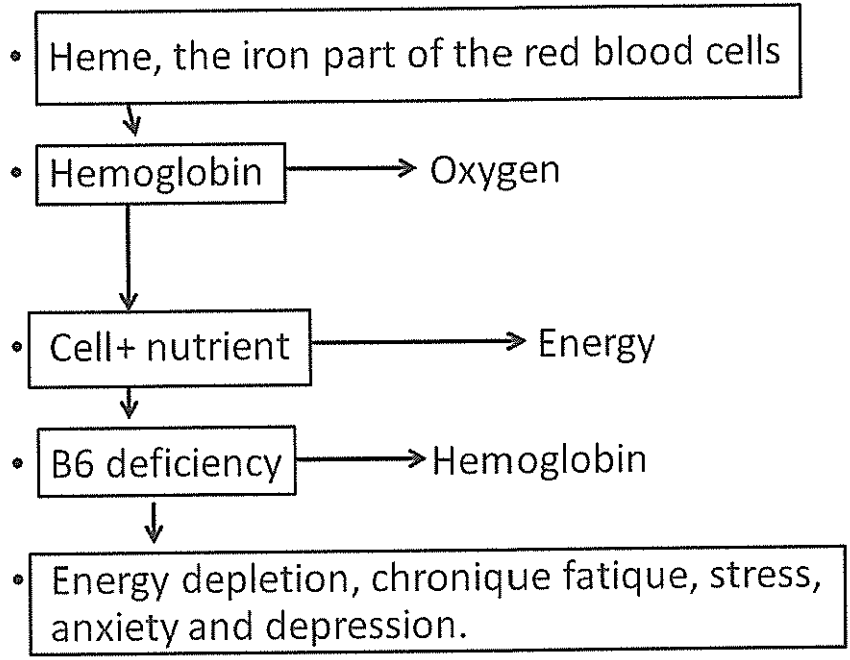


FIGURE 7

Folate deficiency, otherwords, methyl deficient diet, has also been shown to induce apoptosis in tissues including blood. There are several studies that inform about apoptosis in liver cells when these cells are cultured in a folate deficient media (James et al. 1997; Huang et al. 1999). Liver is the main organ to detox body and blood against pathogen microorganisms, allergens and carcinogens. Any failure in liver tissue due to the apoptosis may cause pathogen and carcinogen invasion which increases the risk of cancer formation. These findings indicate that a folate or B_6 deficient diet may increase the cancer risk by causing to apoptosis in liver tissue. Cancer finds its way easier in a weak immun system. Liver protects the immun system and any failure and damage in liver tissue may weaken the immun system and trigger the formation of cancer.

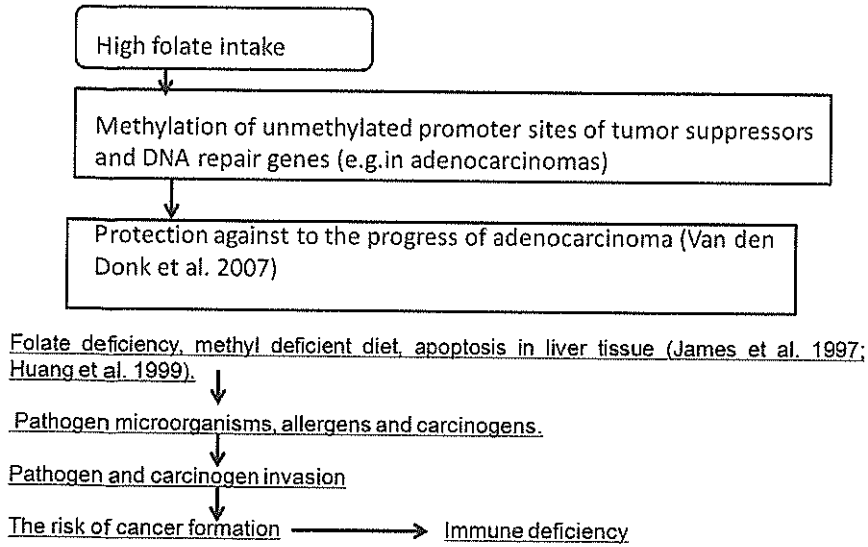


FIGURE 8

Too much folate intake which results in hypermethylation of DNA in cell may be a starting point like hypomethylation of DNA in cell because of folate deficiency as previously indicated. There is a limited number of studies which conflict to each other about the high and low folate or B_6 intakes. For example, one study claims that folate more

than 400 microgram daily reduces the risk of colon cancer in women (Giovannucci et al 1998) while another study claims an increased risk on colon cancer with less than 200 microgram/d folate (Schernhammer et al. 2008). In spite of the limited number of such conflicted studies, we still need to highlight the definite and correct definitions of the high B_6 or folate intakes with more studies.

Garcia-Closas et al. (2007) claim that there is a reverse association between bladder cancer and high fruit intake, folate, B_{12}, B_6 and B_2 while meat or fish intake, their cooking methods or the level of doneness, or heterocyclic amine intakes were not significantly associated with a reduced risk.

Folates and B_6 are very close vitamins in structure and function. Both vitamins maintain genomic stability by regulating DNA biosynthesis, repair and methylation while deficiency of them induce and accelerate carcinogenesis by perturbing these processes (Duthie 2011).

Cancer begins with the change of DNA structure. One carbon atom from B_6 or folate utilizes the methylation of DNA in a healthy cell, meaning that carbon from folate or B_6 forms a methyl group and adds it into the DNA. Either the insufficiency or excess of carbons from B_6 or folate, may cause improper methylation in DNA structure, which may appear as in the form of 'hypomethylation' or 'hypermethylation'. The excess carbon intake from B_6, folate or B_6/folate rich foods may cause excess rate of methylation (hypermethylation) in DNA. Cravo et al. (1994) observed the rectal mucosa from patients with carcinomas as significantly less methylated than in healthy controls. But, Roswall et al. (2010) claimed the opposite that high dose folate supplementation could cause hypermethylation and cancer due to the hypermethylation. But, the high dose which was used in their study was 3.4 times more (325.3 μg) than the median daily supplemental intake which is 100 μg. Both results clearly indicate that either hypomethylation or hypermethilation can cause cancer.

Another example for the polymorphisms which are caused by hypo or hypermethylation is often associated with regular and long term of alcohol consumption. Alcohol is one of the antagonists for folate and other methyl donors; methionine (an essential amino acid which is exist in animal origin foods like; meat, milk, meat and dairy foods, fish and

marine origin foods), vitamins B_6 and B_{12}, B_6 rich foods (e.g. beef liver, tuna, salmon, chicken breast, banana, ground beef, bulgur, squash, nuts, onion, spinach, turkey meat, tofu, raisins and watermelon (USDA, 2011), folate and folate rich foods (e.g. beef liver, spinach, black-eyed peas, asparagus, Mustard greens, green peas, kidney beans, peanuts, crab, orange, yeast, egg, cantaloupe, fish, milk and chicken breast (USDA, 2012) and B_{12} rich foods, e.g. clams, liver, beef, tuna, milk, yogurt, cheese, trout, egg, salmon and chicken breast)(USDA 2011).

Not only alcohol, but also regular and the very rich consumption of B_{12}, folate and B_6 cause the polymorphism of the enzyme, methylentetrahydrofolate reductase (MTHFR) C677T. This enzyme is critical in folate metabolism since it catalyzes the irreversible conversion of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate which is crucial in DNA synthesis. In case of the MTHFR C677T polymorphism, 5,10-methylenetetrahydrofolate can not be converted to 5- methylenetetrahydrofolate which results in the increase of 5,10-methylenetetrahydrofolate (homocysteine) (Kim 2003). 5,10-methylenetetrahydrofolate (homocysteine) is essential for methionine synthesis. Because of the mentioned increase in 5,10-methylenetetrahydrofolate (homocysteine), this substance begins to incorporate with uracil, one of the nucleobases in DNA, extensively. 5,10-methylenetetrahydrofolate supplies more methyl to uracil which causes an extensive incorporation of uracil with methyl, forming the imbalances in deoxynucleotide pools, DNA sturucture and chromosomal breaks in DNA (Christman et al. 1993). These imbalances and breaks in the structure of DNA are responsible for the increased risk of colon cancer (Ames 2001). Briefly, folate, folic acid, B_{12} and homocytein, may be cancer predisposing factors if they are in extremely high doses for long periods, causing hypermethylation and decomposition in DNA since they are methyl donors (Hultdin et al. 2005). This detail is crucial because it indicates to the cancer risk of the food consumptions in heavy amounts which are extremely rich in these vitamins. But, like hypermethylation, hypomethylation also causes DNA decompositions and breaks. DNA hypomethylation is the almost companion to hypermethylation of the genome in cancer and thus, is often associated with cancer (Ehrlich 2009). The initial reason

for the cancerogen potential versus anticancer potential of methyl donor vitamins; B_6, folate, folic acid and B_{12} is that either their insufficient intakes by leading to hypomethylation or their extremely high intakes by leading to hypermethylation can cause cancers via the breaks and decompositions in DNA.

Another mechanism for the increasing risk in cancer formation is the B_6, folate, folic acid and B_{12} deficiency which results in the increase of deoxyuridine monophosphate/thymidylate (dUMP/dTMP) ratios, besides the mentioned uracil misincorporation into DNA (Mashiyama et al. 2008).

Deoxyrudine monophosphate is a nucleotide, a molecule that makes up the structural units of RNA which directs protein synthesis and DNA which controls and transfers genetic characteristics. Like all other nucleotides, the nucleotide serves as chemical energy source as in the form of adenosine triphosphate. Besides, it is incorporated into enzymatic reactions, as being a part of Coenzyme A and flavin adenine dinucleotide and hence it plays an important role in energy production. On the other hand, thymidylate synthetase is essential for regulating the normal DNA replication in healthy cells. The increase in deoxyuridine monophosphate and the decrease in thymidylate synthase due to vitamin B_6 deficiency mean the increase and overload of energy in cancer cells which enhances the degree of cancer invasion and increase in enzymatic activity in cancer cells. Additionally, the decrease in thymidylate in the ratio due to B_6/folate deficiency may cause abnormal DNA replication and cell replication which result in cancer formation (Artinyan et al. 2005; Klubes et al. 1978). Briefly, dose regulation with its control is the basic skleton which should be concerned prior to an evaluation and criticizing whether B_6 or folate has carcinogenic effect. The indicated findings clearly seem to underline that, except the heavy consumptions of foods rich in B_6/folate for long periods or exceeding the daily normal intakes (>100 μg/d), B_6 or folate do not have any cancer triggering effect, while the lack of B_6 or folate or the deficiencies of each vitamin can be a contributor to cancer formation.

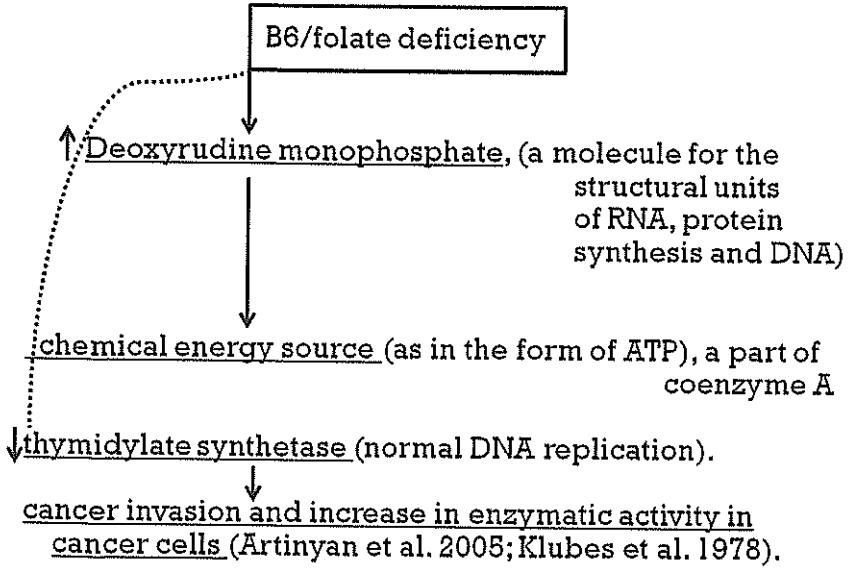


FIGURE 9

The cancer contributing effects of B_6/folate are not only DNA polymorphisms due to the increase in 5,10 methylenetetrahydrofolate or the increase in deoxyrudine monophosphate to increase the energy levels in cancer cells. But also the following mechanisms may indicate to the significant anticancer effects of B_6/folate, provided that if these doses are not higher than >100 μg/d.

Folate degradation produces ROS (Williams et al. 2012) which arises from the possibility of the synergism between folate and the anticancer drugs to kill tumors via ROS production. On the other hand, a very crucial point arises at this point that B_6/folate (and also B_{12} and folic acid) supplementations or the heavy consumptions of the foods highly rich in these vitamins (e.g. beef liver, tuna, salmon, chicken breast, banana, ground beef, bulgur, squash, nuts, onion, spinach, turkey meat, tofu, raisins, watermelon, black-eyed peas, kidney beans, peanuts, crab, orange, yeast, egg, cantaloupe, milk, chicken breast, yogurt and trout) should be avoided or limited during the treatments with the anticancer drugs which target tumors by producing ROS; sunitinib, sorafenib,

tetrandine, cisplatin, bortezomid, vorinostat, MG-132, metformin, thapsigargin, tunicamycin, 17AAG, DBeQ, ritonavir and brefeldin A, since the mentioned vitamins are methyl donors and hence, may cause DNA polymorphisms via the hypermethylation. These anticancer drugs kill tumors and cancerous cells by the ROS which they generate. The significantly high amounts of these ROS generated together with the methyl to uracil incorporations may form DNA breaks which may result in DNA polymorphism and hence cancer, while the ROS and methyl to uracil incorporations may be very toxic on healthy cells (provided that if there is a heavy consumption of foods rich in these vitamins for long periods!). Therefore, during the treatments with the mentioned drugs which produce ROS, the indicated foods which are methyl donors should be limited. Similarly, the same crucial risk appears for the anticancer drugs which induce caspase activity followed by the mitochondrial permeabilization, ROS influx and cytochrome c release, the drugs; costunolide, cisplatin, mitomycin C, garcinol, brefeldin A, valinomycin, piceatannol, kinetin riboside, lipase inhibitor, THL (tetrahydrolipstatin), imiquimod, SC 560, romidepsin, ouabain, digoxin, proscillaridin A, borrelidin, sanguinarine, bortezomib, MT-21, lonidamine, K858, saikosaponin A, CIL-102 and prodigiosin. Here, the most important consideration should be the risk of the harmful effect of the hypermethilation and ROS generation not only on cancer cells, but also on healthy cells. Therefore, the indicated vitamin supplementations or food consumptions rich in these vitamins should definitely be limited during the treatments with the ROS and caspase inducing drugs.

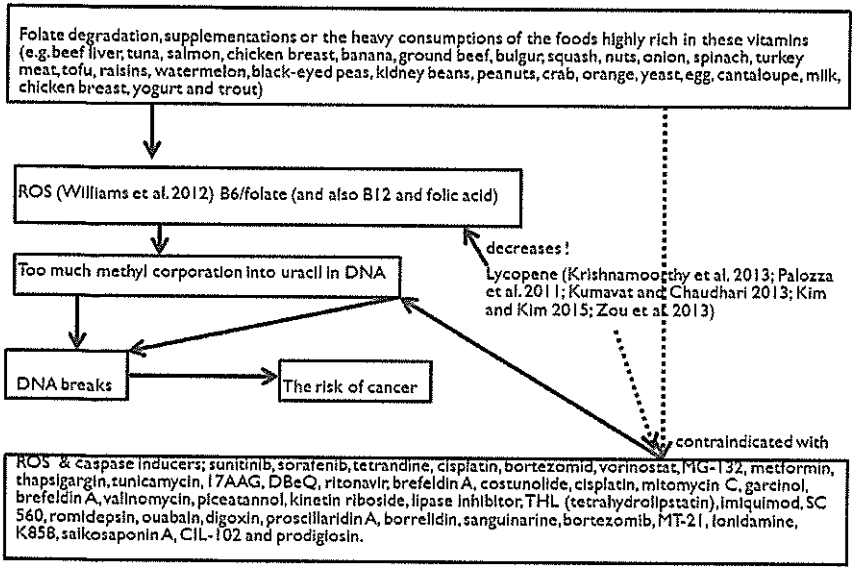


FIGURE 10

B_6 and folate inhibit the activity of COX-2, the enzyme which is responsible for the production of inflammatory hormones (Cutolo et al. 2001; Yanaka et al. 2005). Therefore, the combination of the heavy and long term consumptions of the foods rich in B_6/folate; beef liver, tuna, salmon, chicken breast, banana, ground beef, bulgur, squash, nuts, onion, spinach, turkey meat, tofu, ground beef, lettuce, avocado, broccoli, mustard green, green peas, kidney beans, penuts watermelon, raisins, crab, orange, yeast, egg, cantaloupe, fish, milk and and chicken breast, as combined with the anticancer drugs which inhibit COX-2 activity; sunitinib, celecoxib, magnolol, honokiol, eugenol, bis-eugenol, tetrandrine, 17AAG, raloxifene, rofecoxib, nafroxen, dexamethasone, hydrocortisone, triamcinolone acetonide, methyl prednisolone and beclomethasone diproprionate, may increase the anticancer potential of these anticancer drugs via their synergism to inhibit COX-2.

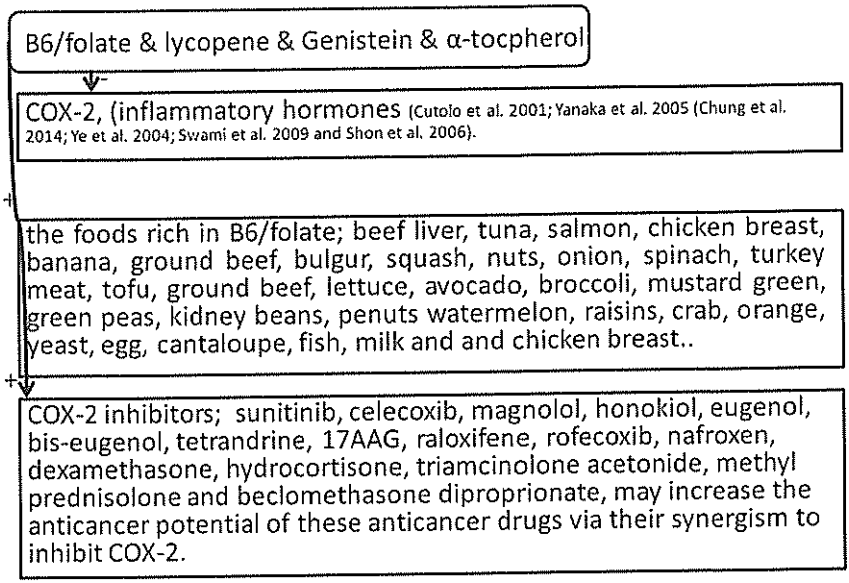


FIGURE 11

Another important point to be concerned under the highlight of the lates findings, vitamin B_6 (pyridoxal 5'-phosphate) elevates the expression of the active form of ERK1, the intracellular protein serine/ threonine kinase which acts as antiapoptotic (Zhang et al. 2013) and thus, supplements of B_6 or the long term food consumptions rich in vitamin B_6 during the treatments which administer ERK inhibitory drugs; varinostat, ritonavir, radicicol, tamoxifen, geldanamycin, lapatinib, fulvestrant, PD98059, U0126, honokiol, SNX212, may decrease the anticancer effects of these drugs. In addition to the B_6 rich foods (e.g. beef liver, tuna, salmon, chicken breast, banana, ground beef, bulgur, squash, nuts, onion, spinach, turkey meat, tofu, ground beef, lettuce, avocado, broccoli, mustard green, green peas, kidney beans, penuts watermelon, raisins, crab, orange, yeast, egg, cantaloupe, fish, milk and and chicken breast), similarly sulforaphane and sulforaphane rich foods; white cabbage, Brussels sprouts, radish, mustard, broccoli, red cabbage, cauliflower, Chinese kale and turnip, should also be limited during the treatments with the mentioned anticancer drugs since the

bioflavonoid induces ERK signaling like B_6, but opposite to beta carotene as previously indicated.

It seems too early to declare that vitamin B_6 has an anticancer effect via the inhibition of ERalpha. There is only one study in this context, claim that there is no any effect of the vitamin on ERalpha, in a cohort study of 848 patients with breast cancer and 28345 control (Lin et al. 2008). But, the limitation of the study only to the women with ≥45 years of age, makes it necessary to have new studies in the field to prove any effect of the vitamin on ERalpha with concrete reasons. On the other hand, serum vitamin B_{12} (but not folate) status was found to be associated with ERalpha (Al-Ghnaniem et al. 2007).

The effect of either folate or B_6 on FOXO3, the gene and transcription factor which triggers apoptosis through the upregulation of other apoptotic genes like Bim and PUMA, still remains unkown since there is currently no study about this association.

Vitamin B_6 (pyridoxal 5'-phosphate) inhibits the activity of AKT, serine/threonine-specific protein kinase, playing crucial role in multiple cellular processes such as glucose metabolism and hence, may induce cancer (Xia et al. 2014). This inhibition may be another explanation for the anticancer effect of the vitamin. For the same reason, the anticancer effects of the anticancer drugs which target tumor cells by inhibiting Akt, e.g. LY29002, SF-1126, NVP-BEZ235, XL147, XL765, ISC-4, GSK690693, MK-2206, fused pyrimidines, phosphatidylinositol (3-5) triphosphate (PIP3), GDC-0941, celecoxib, 7-hydroxystaurosporine (UCN-01), BX-795, BX-912, BX-320, CCT128930, GDC-0068, perifosine, GSK-2141795, GSK2110183, Ipatasertib, Afuresertib, AT13148, PF-04691502, A47867 and triciribine, may increase, if they are administered during the consumption of the foods rich in B_6, e.g. beef liver, tuna, salmon, chicken breast, banana, ground beef, bulgur, squash, nuts, onion, spinach, turkey meat, tofu, ground beef, lettuce, avocado, broccoli, mustard green, green peas, kidney beans, penuts watermelon, raisins, crab, orange, yeast, egg, cantaloupe, fish, milk and and chicken breast, in addition to the beta carotene rich foods; carrot, amaranth, guava, mango, orange, papaya, strawberry, sugar apple, cucumber, green chili, red chili, mint, French bean, resveratrol and resveratrol rich foods; grapes, blueberries, raspberries and mutberries,

sulforaphane and sulforaphane rich foods; white cabbage, Brussels sprouts, radish, mustard, broccoli, red cabbage, cauliflower, Chinese kale and turnip and cinnamon, cinnamon containing foods; Curcuma longa and I3C and I3C rich foods; cruciferous vegetables like broccoli, cabbage, cauliflower, bok choy and Brussels sprouts, since all these vitamins and bioflavonoids inhibit Akt, as being similar to B_6 and the mentioned anticancer drugs.

Although there is no study as related to the relation between B_6 and Hedgehog signaling, the signaling whose overexpression or overactivity may induce cancer, folate deficiency through hypomethylation has been claimed to activate Hedgehog signaling and therefore, enhance the invasiveness of human colon cancer cells (Wang et al. 2012). Based on the findings of the study as related to B_6/folate and Hedgehog signaling, any folate/B_6 deprivation should be avoided, especially during the treatments with the anticancer drugs which inhibit Hedgehog signaling, namely; CUR-61414, HhAntag-691, GDC-0449 (in basal cell carcinoma, medulloblastoma and rhabdomyosarcoma), guggulsterone (a plant steroid, obtained from Commiphora mukul, soridegib(IPI-926) (in advanced solid tumors), phthaladines, namely LY2940680, NVP-LEQ506, itraconazole, an antifungul (in meddulloblastoma), NVP-LDE225, TAK-441, XL-139, HTS piperidines, MRT-83, PF-04449913(acute myeloid leukemia, N-acylethanolamides, 2-acylglycerols and 2-alkylglycerol (endocannabinoids), SANT1-SANT4, CUR-61414, HhAntag-691, GDC-0449, guggulsterone, saridegib, phthaladines, itracanozole, NVP-LDE225, TAK-441, XL-139, HTS piperidines, MRT-92, MRT-83, PF-04449913, N-acylethanolamides, 2-acylglycerols and 2-alkylglycerol. Also, the anticancer diet which consists from resveratrol and resveratrol rich foods like grapes, blueberries, raspberries, mulberries and red wine, genistein and genistein rich foods like; currants, raisins, satsumas, Brazil nut, chestnut, coconut, bazelnut and sesame seeds, curcumin and curcumin rich foods; turmeric and ginger, EGCG (Epigallocatechin gallate) rich foods; white tea, green tea and black tea, dark chocolate, fava beans, pears, raspberries, cherries, blackberries, apples, apigenin and apigenin rich foods like; parsley and celery, baicalein rich foods like; *Scutellaria baicalensis* (or Huang Qin, also known as the Chinese skullcap), carrot, celery and broccoli, quercetin and quercetin rich

foods like onions, kale, broccoli, lettuce, tomatoes, asparagus, red leaf, lettuce and green pepper), during the treatments with the Hedgehog inhibitors; SANT1-SANT4, CUR-61414, HhAntag-691, GDC-0449, guggulsterone, saridegib, phthaladines, itracanozole, NVP-LDE225, TAK-441, XL-139, HTS piperidines, MRT-92, MRT-83, PF-04449913, N-acylethanolamides, 2-acylglycerols and 2-alkylglycerol, should be free from B_6/folate supplementations or the foods rich in these vitamins.

One of the very limited number of studies, to highlight the relation between GRP78, the central regulator of endoplasmic reticulum (ER) and a chaperon with its protein folding capacity, the one which belongs to Kokame et al. (2000), points out an extraordinary disorder and its association with GRP78 and a novel protein, Herp. The authors indicate to the effect of hyperhomocysteinemia on GRP78. Hyperhomocysteinemia, due to the insufficient intakes of vitamin B_6, induces not only GRP78, but also another novel chaperon, Herp. Herp is also induced by mercaptoethanol, tunicamycin, A23187 and thapsigargin. Therefore, during the treatments with these anticancer drugs which target Endoplasmic reticulum (ER) and cause ROS influx as a result of ER stress by Herp, B_6/folate rich foods; beef liver, tuna, salmon, chicken breast, banana, ground beef, bulgur, squash, nuts, onion, spinach, turkey meat, tofu, ground beef, lettuce, avocado, broccoli, mustard green, green peas, kidney beans, penuts watermelon, raisins, crab, orange, yeast, egg, cantaloupe, fish, milk and and chicken breast, may be advisable to be able to inhibit hyperhomocysteinemia (Miodownik et al. 2007), which induces Herp, especially during the administrations of the mentioned drugs. The mentioned diet may be in a synergy with the mentioned anticancer drugs via the inhibition on GRP78 and Herp by preventing the risk of hyperhomocyteinemia, and this may result in the ROS influx and cytochrome c release, leading to the destruction of cancerous cells by ROS and cytochrome c. Therefore, GRP78 and Herp inhibitors; sunitinib, sorafenib, SCH727965, metformin and bortezomid combination, tunicamycin, radicicol, KUSs, versipelostatin, pyrivinium pamoate, eeyarestatin, tanespimycin, mercaptoethanol, thapsigargin and 17-AAG, whose inhibitory effects on these chaperons are determined by Han et al. 2013, Chiou et al. 2010, Abdel Malek et al. 2015, Ikeda et al. 2014, Banerjee et al. 2011, Vogen et al. 2002, Mimura et al. 2012, Sun

et al. 2013, Park et al. 2011, Papandreou et al. 2011, Tashiro et al. 2009, Carew et al. 2013, Kokame et al. 2000 and Krige et al. 2008, may benefit from the mentioned anticancer diet.

Although there is no any study about the effect of folate, the close friend of vitamin B_6, vitamin B_6 has been found to inhibit hem oxygenase-1(HO-1), the enzyme which produces teratogens; carbon monoxide, biliverdin and free iron (Kayashima et al. 2011). Hence, the treatments which target the inhibition of HO-1; tin (IV) protoporphyrin 1 dichloride (SnPP), zinc (II) protoporphrin IX (ZnPP), zinc (II) deuteroporphyrin IX-2, 4 bisethyleneglycol, imidazole-based compounds (8, 9,10R,10S,11,12,13,3), caveolin-1, calcineurin, siRNA, metformin, tin-mesoporphyrin, zinc mesoporphyrin (ZnMP), PEG-ZnPP (pegylated zinc protoporphyrin) and OB-24, may show stronger anticancer potential if they are administered during the food consumptions rich in folate/B_6; beef liver, tuna, salmon, chicken breast, banana, ground beef, bulgur, squash, nuts, onion, spinach, turkey meat, tofu, ground beef, lettuce, avocado, broccoli, mustard green, green peas, kidney beans, penuts watermelon, raisins, crab, orange, yeast, egg, cantaloupe, fish, milk and and chicken breast, in addition to vitamin C and vitamin C rich foods; banana, broccoli, fresh cabbage, spinach, tomato, lettuce, citrose fruits, green lesafy, since both vitamin C and B_6 inhibit HO-1 activity, similar to the mentioned anticancer drugs.

The effect of vitamin B_6 or folate on p38, the enzyme which prevents apoptosis, as being depended on the stimuli and cellular context, is still unknown, waiting to be highlighted.

Antimalarial drugs that can cause acute hemolysis in people with G6PD deficiency, namely; DHEA (dehydroepiandrosterone), 6-AN(6-aminonicotinamide), the novel derivatives of the steroid DHEA1 which are produced by androstane nucleus with a pregnane nucleus and pregnan-20-ones incorporation of 21-hydroxyl group, chloroquine, Flutamide and rasburicase, pamaquine, primaquine, sulfonamides; e.g. sulfanilamide, sulfamethoxazole, thiazosulfone and mafenide), analgesics; e.g. aspirin, phenazopyridine and acetanilide, and a few non-sulfa antibiotics; e.g. nalidixic acid, nitrofurantoin, isoniazid, dapsone and furazolidone, should be avoided in the treatments of patients with cancer as they are in antagonism with folate synthesis (Frank 2005). On

the other hand, B_6/folate and the foods rich in these vitamins appear as novel protective nutrients in the current status of cancer nutrition since they may help for the better prognosis of cancer patients who have already G6DP deficiency or who are suffered with the deficiency in the later periods of cancer. For the same reason, the treatments with steroid DHEA1, DHEA chloroquine, flutamide and rasburicase which induce apoptosis by inhibiting G6PD may require more consumption of B6/ folate rich foods in the periods after the treatments, opposite to vitamin C and vitamin C rich foods which may worsen the G6PD deficiency characterized by fatique and anemia, if these vitamin C rich foods/ supplements taken in high amounts, during or after the treatments with the mentioned anticancer drugs.

One of the novel anticancer treatments which aim the prevention and inhibition of metastasis is nitric oxide (NO). Depending on the level of NO which is released and sustained, NO may act as anti-tumorigenic by inhibiting hyperactivated cell survival/anti-apoptotic pathways like the activity of NF-kB, transcription factor which makes cancer cells more resist against both chemotherapeutic and immunotherapeutic drugs, and the inhibition of Raf-1/MEK1/2/ERK1/2 (the extracellular signal regulated kinases) to control cell proliferation and survival. Though there is a conflicting data as related to the pro-tumorigenic effect or anti-tumor effect of NO (Wink et al. 2008), such conflicting data may be resolved by the findings that elevated levels of endogenous NO in tumor tissues are pro-tumorigenic while Nitric oxide synthases(NOS), a group of enzymes which produce NO, inhibits tumor growth. The overexpression of NO stimulates and activates NOS, activating the cell death (Gauthier et al. 2004). The inhibition of angiogenesis and tumor growth by the overexpression of NO which was informed by Jones et al. (2004) is the backbone of the novel anticancer drugs; the NO donors, namely; DETANONOate, NCX-4040 (Tesei et a. 2008), NO-donating non-steroidal anti-inflammatory drugs (NO-NSAIDs) (Rigas and Williams (2008), sodium trioxodinitrate (Angeli's salt, P-nitrosophosphate compounds (Ignarro et al. 2002 and Ware and King 2000), NO gas, as being freely soluble in physiological solutions (but its use has been limited to inhalation therapy because of its short half-life and rapid reactivity toward molecular oxygen) (Nelin and Hoffman

1998), diethylamine/NO and diethylenetriamine/NO (Keefer et al. 1996), diazeniumdiolates (Fernandez-Tome et al. 1999), oxatriazolium and furoxan compounds (Schonafinger 1999), sydnonimines (Feelisch 1998), S-nitrosothiols (Jaworski et al. 2001). On the other hand, vitamin B_6 has been claimed to increase nitric oxide synthesis (Friso et al. 2001; Matsubara et al. 2003). The increase in nitric oxide by the vitamin may be helpful to improve the anticancer potential of these novel anticancer drugs; the NO donors. Therefore, B_6/folate rich foods; beef liver, tuna, salmon, chicken breast, banana, ground beef, bulgur, squash, nuts, onion, spinach, turkey meat, tofu, ground beef, lettuce, avocado, broccoli, mustard green, green peas, kidney beans, penuts watermelon, raisins, crab, orange, yeast, egg, cantaloupe, fish, milk and and chicken breast, may improve the anti-tumorigenic effect of the NO donors, since both these drugs and foods may create a synergism to increase the amount of nitric oxide to kill cancer cells. But, PDE5Is (phosphodiesterase-5 Inhibitors) which are used for the treatment of erectile dysfunction or pulmonary hypertension by inhibiting phosphodiesterase-5, the enzyme that accepts cGMP (cyclic guanosine monophosphate, a messenger to relax smooth muscle tissues, vasodilation and increased blood flow and breaks it down) are administered as combined with NO donors, both NO donors and PDE5Is (e.g. sildenafil, vardenafil, tadalafil) increase cGMP. The excess accumulation of cGMP can lead to a severe vasodilation and hypotension (Emmick et al. 2002; Scicinski et al. 2015), which should be taken into consideration as an important side effect during the anticancer treatments by NO donors and B_6/folate rich foods as combined with the treatments using PDE5Is. But, although NO induction by using NO donors has appeared as one of the novel anticancer treatments, an important amount of data indicates to the cancerogenic effect of it (Thomsen et al. 1995; Reveneau et al. 1999, Loibl et al. 2002). While the paradox whether NO is cancerogen or anticancerogen still continues, one of the most significant findings indicate to the alteration of the cell morphology in cancer stem cells via the NO exposed lung carcinoma cells with or without the administration of NO donor, S-nitroso-N-acetylpenicillamine), leading to the aggressive behavior of the cells (Yongsanguanchai et al. 2015). While such treatments are controversial and still under debate, vitamin C, I3C, apigenin, genistein,, resveratrol,

sulforaphane, kaempferol, myricetin, beta carotene, EGCG and curcumin inhibit the signaling molecule (TGakahashi et al. 2009, Jang et al. 2009, Erdogan et al. 2007, d'Uscio et al. 2003, Rostoka et al. 2010, Rathel et al. 2005, Zheng et al. 2004, Mu et al. 2001, Hur et al. 2013, Rostoka et al. 2010 and Singh et al. 2002).

THE STUDIES as RELATED to THE ASSOCIATION of B6/ FOLATE and CANCER

- 121.701 women/30-55 years of age/12 years of follow up/ smoking adjusted, alcohol adjusted/≥59 ng/mL plasma folate concentration as the highest quartile (1.22, 0.77-1.95, 95% CI) versus≤53 ng/mL as the lowest quartile (R:1.00, 95% CI) and ≥49 pmol/mL plasma B_6 concentration (0.87, 0.55-1.37, 95% CI) versus ≤41 pmol/mL (R:1.00, 95% CI) decreased the risk of pancreatic cancer (Schernhammer et al. 2007).
- 55557 men and women/721 lung cancer/10.6 years of follow up/ smoking adjusted, alcohol adjusted/15.745 μg/d(1.37, 1.01-1.84, 95% CI) as the highest quartile of folate/folic acid intake versus 181 μg/d (R:1.00, 95% CI) as the lowest, increased the risk of lung cancer!!! (Roswall et al. 2010).
- 51529 men/30-75 years of age/1980-2008/smoking adjusted, alcohol adjusted/805 μg/d total folate intake as the highest quartile (0.73, 0.63-0.86, 95% CI) versus 245 μg/d (R:1.00, 95% CI) as the lowest did not make any effect on the risk of colorectal cancer (Zhang et al. 2012).
- 44410 men, 86440 women/28 year follow up/max mean level of PLP (pyridoxal 5-phosphate) plasma were 98. 3 pmol/mL in women and 183.2 pmol/mL in men while the lowest mean concentrations were 38.8 pmol/mL in women and 66.0 pmol in men. The higher plasma PLP concentration caused 20 to 30 % lower risk of colorectal cancer (Zhang et al. 2012)
- 121701 women/399 colon cancer/30-55 years of age/22 years of follow up/smoking adjusted, alcohol adjusted/<200 μg/d (0.54, 0.36-0.81, 95% CI) versus 200-299 μg/d (0.42, 0.24-.076, 95% CI) decreased the risk of colon cancer(Schernhammer et al. 2008).
- 208 pancreatic cancer/623 control/No relation between folate and pancreatic cancer (Schernhammer et al. 2007)

- 1997-2002 714 cancer patients who use vitamin supplements including B_6 and 415 non user cancer patients/supplement use decreases the risk of lung cancer (Jatoi et al. 2005)
- 35.023 women/743 breast cancer/2000-2006/50-76 years of age/ alcohol adjusted, smoking not adjusted/450-483 μg/d as the highest quartile of daily folate intake (0.91, 0.68-1.22, 95% CI) versus the lowest, 37-260 μg/d /R:1.00, 95% CI) decreased the risk of breast cancer (Maruti et al. 2009)
- 899 lung cancer/1770 control /(1992-2006/Dietary vtamin B_6 decreased the risk/(Johansson et al. 2010)
- The highest vitamin B_6 intake (0.51, 0.38-0.69, 95% CI) versus the lowest (0.90, 0.75-1.07, 95% CI) decreased the risk of colorectal cancer in the meta analysis of 9 studies (8 cohorts ana 1 nested case-control) 1980-2009/34-84 years of age decreased the risk (Larsson et al. 2010)
- 712 breast cancer/712 control/1989-1996/B6 decreases the risk of colorectal cancer (Zhang et al. 2000)
- 721 lung cancer/10.6 years follow up, high intake of folate increases the risk of lung cancer (Roswall et al. 2010)
- 1129 lung cancer/1997-2002/B_6 supplementation decreases the risk of lung cancer (Jatoi et al. 2005)
- 964 men/31 prostate cancer/31 prostate cancer/20 years of follow up/smoking adjusted, alcohol adjusted/>2 μg/L(4.79, 1.56-14.43, 95% CI) versus ≤2 μg/L(1.56, 1.05-2.38, 95% CI) decreased the risk (Rossi et al. 2006)
- 399 colon cancers/<200 microgram/d increases the risk of colorectal cancer (Schernhammer et al. 2008) by increasing the risk of the overexpression of p53 which is a tumor suppressor protein as encoded by the TP 53 gene.
- 65 bladder cancer/B_6 (200mg/d) for 10 months reduced the recurrence (Lamm et al. 1994).
- 532 pancreatic cancer, 1701 control, 1995-1999/B_6 reduced the risk/alcohol adjusted, smoking adjusted/≥738 μg/d folate supplementation (0.67, 0.48-0.93, 95% CI) versus <280 μg/d (R:1.00, 95% CI) (Gong et al. 2009).

- 224 colorectal cancer, 411 control, 67.594 men and women, 2001-2006/smoking adjusted, alcohol adjusted/>26.1 ng/mL plasma folate concentration (0.61, 0.33-1.13, 95% CI) versus ≤9.94 ng/mL(R:1.00, 95% CI) decreased the risk of colorectal cancer (Le Marchand et al. 2009)
- 442 colon cancer/ 88756 women/1980-1994/smoking adjusted, alcohol adjusted/folate (>400 μg/d(0.69, 0.52-0.93, 95% CI) versus ≤200 μg/d (R:1.00, 95% CI) decreased the risk (Giovannucci et al. 1998)
- 47.931 men/ 205 colon cancer/ 6 year of follow up/smoking adjusted, alcohol adjusted/>400 μg/d(0.69, 0.52-0.93, 95% CI) versus ≤200 μg/d (R:1.00, 95% CI) decreased the risk (Giovannucci et al. 1995)
- 987 men ana women/ men-women with colorectal carcinomea/1994-2004/smoking adjusted, alcohol adjusted/≤8.4 ng/mL plasma folate concentration(R:1.00, 95% CI) versus 19 nmol/L(1.13, 0.93-1.37, 95% CI) had no effect (Cole et al. 2007)
- 120852 men ana women/760 colon, 411 rectal carcinoma/7.3 years follow up/smoking adjusted, alcohol adjusted/55-69 years of age/>266 μg/d folate intake as the highest quartile (0.93, 0.57, 95% CI) versus <168 μg/d as THA lowest(R:1.00, 95% CI) decreased the risk of only rectal carcinoma, not colon cancer (Konings et al. 2002)
- 828 colon cancer, 428 rectal cancer/ 2024 control/40-74 years of age//1985-1992/69 μg/d as the lowest (R:1.00, 95% CI) versus 404 μg/d as the highest quartile of folate intake(0.40-0.68, 0.52, 95% CI) decreased the risk (Ferraroni et al. 1994)
- 428 colon cancer, 372 rectal cancer/1975-1986/folate decreased the cancer promoting risk of alcohol (Freudenheim et al. 1991)
- 11699 women, 392 women breast cancer/, 1023 colorectal cancer/≥50 years of age/1991-2003/alcohol adjusted, smoking adjusted/302 μg/d as the highest quartile of folate intake (0.93, 0.67-1.29, 95% CI) versus 153 μg/d (R:1.00, 95% CI) decreased the risk (Ericson et al. 2007)
- 43512 men and 56011 women with colorectal cancer/1999-2007/50-74 years of age/smoking and alcohol

adjusted/≥316 µg/d as the highest quartile of natural folate intake (0.99, 0.74-1.32, 95% CI) versus the lowest, <198 µg/d (R:1.00, 95% CI) in men with the ROs for women (0.86, 0.70-1.06, 95% CI versus R:1.00, 95% CI) decreased the risk (Stevens et al. 2011)

- Meta analysis of prospective studies by a search of MEDLINE and EMBASE databases to February 2010/B_6 and pyridoxal 5-phosphate (PLP) intake decrease the risk of colorectal cancer (Larsson et al. 2010).
- 61.433 women, 805 colorectal cancer/40-76 years of age/14.8 year follow up/smoking adjusted, alcohol adjusted/≥2.05 mg/d as the highest quartile of vitamin B6 intake (0.77, 0.62-0.97, 95% CI) versus <1.53 mg/d as the lowest (R:1.00, 95% CI) decreased the risk (Larsson et al. 2005)
- 61433 women/149 colorectal adenoma/286 control/18-75 years of age/smoking and alcohol adjusted/1997-2002/>183 µg/d as the highest quartile (3.25, 0.55-3.22, 95% CI) versus <183 µg/d (1.04, 0.49-2.22, 95% CI) decreased the risk (Van den Donk et al 2007)
- 73 bronchial metaplasia/4 moths follow up/Folate intake made a significant improvement (Heimburger et al. 1988)
- 38 bronchial metaplasia/24 control/36-79 years of age/ smoking adjusted, alcohol not/1 year follow up/8.6±4.6 ng/mL in non smokers versus 5.6±2.5 ng/mL decreased the risk of lessions in the metaplasi (but ORs are not referred in the published paper!) (Saito et al. 1994)
- 385747 men and women, 899 lung cancer, 1770 control/1992-2000/35-79 years of age/alcohol adjusted, smoking adjusted/the highest quartile of vitamin B_6 (57.8-629 nmol/L) (0.44, 0.33-0.60, 95% CI) versus the lowest quartile (22.5-395 nmol/L)(R:1.00, 95% CI) decreased the risk (Johansson et al. 2010).
- 846 lung cancer, 846 control/1996-2004/smoking adjusted, alcohol not/30-79 years of age/≥100.2 mg/d folate intake (0.32, 0.18-0.58, 95% CI) versus <100.2 mg/d (0.84, 0.56-1.25, 95% CI) decreased the risk of lung cancer (De Stefani et al. 2008).

- 1225 colon cancer, 728 rectum cancers, 4154 control/1992-96/23-74 years of age/229-887 μg/d (0.81, 0.66-1.01, 95% CI) as the highest quartile of daily dietary folate intake versus 255-785 μg/d(R:1.00, 95% CI) in colon cancer, 126-887 μg/d(0.59, 0.45-0.77, 95% CI) versus 182-785 μg/d(R:1.00, 95% CI) in both colon and rectum cancers decreased the risk (La Vecchia et al. 2002)
- 4.2 years of follow up/amoking adjusted, alcohol adjusted/2500 randomly selected women (age: 25-74 y) low serum folat (<6.8 nmol/l) (0.37, 0.11-1.16, 95% CI) versus ≥6.8 nmol/L serum folate (0.36, 0.14—1.91) decreased the risk the risk of colorectal cancer (Guelpen et al. 2006)
- 2028 colorectal cancer, 2722 control men and women (age: ≤55 y)/1 year follow up/ dietary and supplemental intakes of B_6 in diet decrease the risk of colorectal cancer (Theodoratou et al. 2008)
- 25400 women/55-74 years of age/691 breast cancer/1993-2001/ alcohol adjusted, smoking adjusted/≥400 microgram/d(1.19, 1.01-1.41, 95% CI) versus no folic acid supplementation (R:1.00, 95% CI) did not make any change (Stolzenberg-Solomon et al. 2006)
- 32826 men and women, 194 colorectal cancer, 410 colorectal adenoma/1989-1990/ low dietary and low plasma serum B_6 increase the risk of colorectal cancer and colorectal adenoma (Wei et al. 2005)
- 144 colon and rectum cancer/276 control/50-69 years of age/1988-1992/alcohol adjusted, smoking adjusted/159 μg/d (R:1.00, 95% CI) versus 249 μg/d(2.94, 0.84-10.33, 95% CI) decreased the risk (Glynn et al. 1996).
- 3.3 mg/d B6 intake decreases the risk of breast cancer (age: ≥50 y) (Ericson et al. 2007). >400 microgram reduces the risk of colon cancer(Giovannucci et al. 1998). ≥400 microgram intake reduced the risk breast cancer (Stolzenberg-Solomon et al. 2006)
- 41836 men and women/55-69 years of age/598 colon, 123 rectal cancer/alcohol adjusted, smoking adjusted/1986-1998/≥634 μg/d (1.12, 0.77-1.63, 95% CI) versus ≤231 (the lowest highest

quartile (R:1.00, 95% CI) decreased the risk of colon cancer (Harnack et al. 2002)

- 81184 men, 526 colorectal cancer/1995-2002/48-53 years of age/ smoking adjusted, alcohol adjusted/246 g/d folate as the lowest quartile of folate intake (R:1.00, 95% CI) versus 461 g/d as the highest (0.93, 0.56-1.54, 95% CI) and 1.75 mg/d B_6 as the lowest (R:1.00, 95% CI) versus 5.2 mg/d as the highest (0.69, 0.41-1.14, 95% CI) did not make any effect on the risk of colorectal cancer while B_6 significantly reduced the risk of colorectal cancer (Ishihara et al. 2007)
- 29133 men/50-69 years of age/1985-1988/152 colon cancers and 126 rectal cancers/1371 control/ B_6 plasma concentration was found responsible for the cancer cases while 77.7 pmol/ mL plasma B_6 concentration(0.91,0.35-2.42,95%CI)(the highest quartile)versus12.7 pmol/mL(R:1.00, 95% CI) (the lowest quartile) decreased the risk (Weinstein et al. 2008).
- 1365 colorectal cancer/2319 control/men and women/smoking adjusted, alcohol adjusted/1992-1998/>11.3 nmol/L (1.30, 0.67-2.51, 95% CI) plasma folate concentration versus <11.3 nmol/L (1.33, 0.87-2.03) did not any effect (Eussen et al. 2010).
- 3483 breast cancer/16 year follow up/smoking adjusted, alcohol adjusted/30-55 years of age /≥600 µg/d folat intake (0.91, 0.82-1.01, 95% CI) versus <150 µg/d (1.09, 0.89-1.32, 95% CI) decreased the risk (Zhang et al. 1999)
- 3898 postmenopausal breast cancer, 70656 postmenopausal women/1992-2005/ plasma folate concentration in the highest quartile (312.1 microgram/d) when compared with the lowest quartile (166.9 microgram/d) increased the risk (Stevens et al. 2010)
- 712 breast cancer, 32826 women/1989-1996/30-55 years of age/alcohol adjusted, smoking not/ >14 ng/mL plasma folate concentration (0.69, 0.49-0.98, 95% CI) when compared with <4.6 ng/mL (R:1.00, 95% CI) ng/mL decreased the risk (Zhang et al. 2003)

Xun et al. (2011) did not study the relation between any type of cancers and Selenium but they determined the relation between each of the habits of smoking, alcohol, age, gender, ethnicity, region, education and the selenium toenail concentration. They determined the habits of smoking and alcohol as the most significant factors among others that affect the selenium toenail concentration (0.691 μg/g as the lowest quintile of Se toenail concentration/0.65, 0.64-0.65/CI 95% versus 1.037 μg/g as the highest quintile of Se toenail concentration/1.11, 1.09-1.12/ CI 95%).

In spite of the nonsignificant effect of dietary selenium intake on cancer, high selenium levels of selenium in body fluids is often associated with lower cancer mortality. Alaejos et al. (2000) found a nonsignificant effect of dietary selenium intake on various types of cancers in their Meta analysis. The reason for the nonsignificant effect of dietary selenium intake on cancer in spite of a significantly important anticarcinogenic effect of body fluid selenium on cancer may be due to the food origin selenium antagonistic elements which inhibit the anticarcinogenic effects of selenium and also some other antioxidant micronutrients such as ascorbic acid, retinol, beta carotene and alpha tocopherol. Another reason is the primary risk factors that inhibit or shadow the anticarcinogenic effect of dietary selenium in such cohort studies and meta analysis are smoking, alcohol, age, gender, the diet itself (Clark and Alberts 1995), high intake of fat (Virtamo et al. 1987), disease that alter selenium metabolism and influence the selenium rich food dietary intake (Levander 1987), the lack of precision and specificity due to the insufficient measurements of micronutrient intakes through simple dietary questionnaries and current food-composition tables, attribution of cancer risk to a single food constituent, complex metabolic regulations due to circulation of nutrients and different dietary intakes (Riboli et al. 1996). Among all these risk factors which may be the reasons for the findings in cohorts and meta analysis informing the non significant anticarcinogenic effects of dietary selenium, the most

significant ones are the habits of alcohol and smoking, high intakes of dietary fat and protein in animal origin (Schultz and Leklem 1983; Pothier 1987). The increased intake of foods in animal origin which leads to globulin increase that form selenoproteins (like an important antioxidant enzyme, glutathione peroxidase) in plasma may also decrease the free plasma selenium concentration (Takahashi, Newburger and Cohen 1986).

Most of the invivo studies, which were carried out by using rats, as in contrast to the nonsignificant importance of anticarcionegnic effect of dietary selenium due to the mentioned risk factors above, found an importantly significant anticarcinogenic effect of dietary selenium. Organoselenium compounds namely diallyl selenide and benzyle selenocyanate were found to have anticarcinogenic effect on 7,12-dime thylbenzaanthracene (DMBA) induced mammary adenocarcinomas, azoxymethane induced colon cancers and benzoapyrene induced forestomach tumors in mice, indicating to the importance of the mentioned potent cancer chemopreventive selenium compound synthesis by selenium rich foods like garlic and other related allium foods, onion and leeks (El-Bayoumy et al. 2006).

The feeding of rats with the diets containing 1.0 and 2.0 microgram Se/g as selenized broccoli for 2 weeks decreased the incidence of aberrant crypts (AC) (the abnormal tube-like glands in the lining of the colon and rectum as one of the earliest changes in the colon that may lead to colon cancer) and aberrant crypt folci (ACF) (the primary tumor lesions which may be indicative of colon cancer) on rats when compared with the diets low in selenium or the diets that contains no selenium or the diets without selenium in the study of Finley, Davis and Feng (2000). One of the barriers that restrics the use of selenium as a dietary anticarcinogen supplement, may be the accumulation of many selenium forms in tissues or its use in the formation of glutathione peroxidase. But, it was claimed in the study that there was no accumulation of selenium broccoli either in tissues or the increase in glutathione peroxidase activity. According to the authors, selenium in broccoli may be metabolized in a manner that diverts much of the selenium into a pool that provides protection against colon cancer. Although, the material studied is rat, the findings of the study may indicate to the anticarcinogenic potential of dietary

selenium, in broccoli or another food, on human being which should be taken into consideration in future studies. Confirming the findings of the authors, Ip and Hayes (1989) also found a higher bioavalibility of selenomethionine pools in blood, skeletal muscle and glutathione peroıxidase in rats with dimethylbenzaanthracene-induced mammary tumors as compared to selenite. Although their findings are belong to an animal study, it may indicate to the same important superior anticarcinogenic potential of selenomethionine (other words, dietary selenium) and thus the anticarcinogenic potential of selenomethionine rich broccoli, other members of Brassica family and some other foods like onion, garlic and leek.

One study among others, carried out by Tolman et al. (2008) may highlight the reason for the restricted and non significant anticarcinogenic effect of dietary selenium. According to the authors dietary selenium may show its anticarcinogenic effect as combined with isoflavone existence rather than their alone existences in foods.The combined existence of isoflavon and selenium results in lower serum leptin (an antiobesity protein which helps to decrease fat ratio), lower serum IGF-1 (Insulin like Growth Factor, a hormone that may lead to cell fattening) and lower weight gain, all of which may contribute to a significant anticarcinogenic potential of selenium and isoflavone rich food. Thus, isoflavone content of the food should also be concerned in determining Se anticarcinogenic potential as another factor in addition to the mentioned ones above that poor isoflavone content may reduce the anticarcinogenic effect of the mineral whereas high isoflavone content may increase. The same authors noted that the period for selenium was another factor to affect the anticarcinogenic effect of selenium that these periods were also differently affected serum leptin, IGF-1 and eiwght gain. As a result, timing of Selenium supplementation or its dietary intake should also be concerned as another factor determining the selenium anticarcinogenic potential.

Some detailed studies revealed the following 12 distinct mechanisms which may yield the anticarcinogenic effect of the mineral. These are; 1. The inhibitory effect of the mineral on lypoxygenases, the enzymes that produce inflammatory molecules which then be converted into carcinogenic substances that promote cancer growth. For example,

β-lymphocytes express 5-lipoxygenase protein and suppression of cellular 5-lipoxygenase activity is serum dependent and this serum effect can be mimicked by selenium. The selenium dependent inhibition of 5-lipoxygenase activity was observed in the existence of glutathione (one of the selenium dependent enzymes) (Werz and Steinhilber 1996). Similarly, injection of rats with 500 μg/Kg selenium raised leukocyte phospholipid hydroperoxide-glutathione peroxidase activity 8-fold and produced significantly less lipoxygenase metabolites than controls (Weitzel and Wendel 1993). 2. Acting as a cofactor for several key antioxidant enzymes called selenoproteins namely glutathione which may protect from cancerogenic substances in healthy persons without cancer, but not for the patients with cancer especially during their cancer treatments, chemotherapy and radiation. Because elevated glutathione levels increase antioxidant capacity and resistance to oxidative stress in cancer cells like it does in healthy cells and thus increases the resistance of cancer cells to tumor killing peroxy radicals of chemotherapy drugs and radiation (Vojislav et al. 2001; Balendiran et al. 2004; Traverso et al. 2013). These findings should not be evaluated that selenium is carcinogenic since it enhances the production rate of selenium dependent enzyme glutathione which increases the resistance of cancer cells to cancer treatments. If selenium is taken during cancer treatments by patients with cancer, the findings may be important to be concerned and may indicate to such potential of the mineral. This point seems correct for only cancer period but not for healthy persons without cancer. What seems clear about the mineral is that except cancer and its treatments, the mineral increases the antioxidant selenium dependent enzyme glutathione that increases the resistance of the healthy cells to peroxy radicals and therefore may protect these healthy cells against DNA mutations caused by these radicals which may result in cancer. 3. Acting as an antioxidant directly that decreases the amount of free toxic radicals which may be converted into carconiogens. The mineral is used for synthesis of an important antioxidant enzyme, selenium dependent glutathione peroxidase which degrades hydro and lipoperoxides and thus prevents oxidation and free toxic radical production (Gorozhanskaya et al. 2013). Some other selenoproteins besides selenium-dependent glutathione peroxidase have also been found as antioxidant including

the endothelium protection against peroxynitrite-mediated toxicity. The reaction between nitric oxide (the gas produced by amino acid called L-arginine and released during the enzymatic convertion of the amino acid into another amino acid, L-citrulline by the enzyme, nitric oxide synthase) and superoxide anion produces highly reactive hydroxyl radicals promoting the development of oxidative stress and thus inducing cytotoxic effect on cells. Selenium dependent glutathione peroxidase inactivates peroxynitrite and as a result prevents a possible oxidation which involves peroxynitrite. The selenium dependent enzyme reduces toxic peroxynitrite (ONOO-) in cancer potential (Pacher et al. 2007) to nitrite-anion (NO_2) by formation of selenic acid. Therefore, selenium appears as a key mineral not only to prevent organic peroxide centered oxidation, but also the oxidation caused by peroxynitrite. 4. Protection against cancer and inflammation with some of its special mechanisms. The mineral inhibits metastasis by some special mechanisms like forming special anticarcinogen antioxidant selenoenymes as mention above but also thioredoxin reductase to inhibit inflammatory and carcinogenic responses caused by IL-8 (aprotein produced by macrophages), IL-6 (another inflammatory toxic protein produced by muscle cells), MCP 1 (special proteins that yield an inflammatory response by regulating the migration and infiltration of monocytes and microphages) and COX-2 (an enzyme that acts to speed up the production of some chemical messages which trigger tumor growth). IL-6, MCP-1, COX-2 are regulated by a common transcription factor, NF-αβ which is sensitive to intracellular redox status, other words, oxidation and NF-αβ can be inhibited by cellular antioxidant enzymes which is produced by the mineral, selenium. The two selenoenzymes, glutathione peroxidase and thioredoxin reductase depend on the mineral to block NF-αβ. Confirming this, the selenomethionine supplementation diet (3 ppm) in mice reduced breast cancer primary tumor growth and decreased overall tumor burden in major organs, lung, liver, kidney and femur (Mastro et al. 2012). 5. Protection of the circadian expression of genes which are essential to normal cell growth and differentiation (Cry 1, Cry 2, Per 1, Per 2; the proteins that are involved in circadian rhytms, osmotic pressure of cell and in the sensing of magnetic fields, D-binding protein, also known as group specific component-globulin, a protein which binds

to vitamin D and transports to target tissues (Fang, Zhang and Zarbl, 2010). Similarly, the risk of single-nucleotide polymorphisms in the marker genes of prostate cancer, SEP15 and rs5859 were informed to be significantly associated with prostate cancer mortality while there is a significantly important protective effect of selenium to prevent the polymorphism of these genes. Thus, the findings of the case-control study suggest the possibility that some men with prostate cancer may benefit more selenium than others (Penney et al. 2010). 6. Enhancement of the resistance to cancer risk by improving and activating the immune competence and resistance to viral and bacterial infections. The supplementation with Se (100 µg/d) was informed to enhance plasma Se concentrations, lymphocyte cystosolic GPX (an important antioxidant enzyme that scavange hydrogen peroxide in mammalian cells), increased activity in phospholipid GPx-4 (a seleno-glutathione peroxidase, the other important antioxidant that reduces lipid hydroperoxides in cell membranes (Januel et al. 2006), increase in the production of IFN-g, a soluble cytokine with antiviral, immunoregulatory and antitumor properties which is also a potent activator of macrophages and increased T cell proliferation to antigen stimulation (Broome et al. 2004) in adult human subjects with low Se levels (<1.2 µmol/L). But the type of selenium to make the cancer prevention by the mentioned mechanisms should always be taken into consideration since it is one of the most important factors that determine the anticarcinogenic potential of the mineral. Confirming this, organic Se (selenomethionine) is determined to have greater anticarcinogenic potential (Chen et al. 2013). Also, gender, region, ethnicity, education, alcohol and smoking are the main factors that affect the selenium status and thus the anticarcinogenic potential of the mineral. Among these factors, alcohol and smoking are the two most significant effective habits on selenium status (Xun et al. 2011), in addition to the factor of 'mineral form'. Therefore, the involvement of the mineral form and the habits of alcohol and smoking may significantly increase the accuracy of the studies and meta-analysis to determine the anticarcinogenic potential of the mineral 7. Detoxification of cancer-inducing metals. Age corrected breast cancer mortalities in different countries are inversely correlated with the dietary intake of Selenium and directly correlated with the intake of

cadmium, zinc and chromium, suggesting that the anticarcinogenic properties of selenium are counteracted by these elements (Schrauzer, 2008; Drach et al 2005; Wahba et al. 1993; Anetor et al. 2008). 8. Induction of protective 'phase II' liver enzymes such as dimethyl diselenide, 2.5-diphenyl-selenophene, dibenzyl diselenide, methylseleninic acid, benzeneseleninic acid, benzene selenol, triphenylselenonium chloride and ebselen doubled quinone reductase, all of which are produced in liver that reduce carcinogenic quinines and adrenochrome to the non toxic compounds and activate glutathione-S-transferase (another selenium dependent antioxidant enzyme with anticarcinogenic effect) in group of murine Hepa1c1c7 hepatoma cells (a suitable in vitro system for investigating the regulation of chemoprotective enzymes by selenazolidines, the novel L-selenocysteine prodrugs developed as potential chemoprotective agents) (El-Sayed et al. 2007; Xiao and Parkin, 2006). 9. Modulation and shutting down of the essential cell replication cycle needed by cancer cells to support their growth and invasion. Treatment of human prostate cancer cells; LNCaP, PC3-AR2, PC3, PC3-M, DU145, glioma (a type of tumor that starts in brain os spine which is also called as anaplastic astrocystoma) and HCT116 colorectal carcinoma cells with seleno-DL-methionine, methylseleninic acid, methylselenol, sodium selenite and methylselenol caused an arrest in the first period of cancer cell proliferation (G1 phase), apoptosis and reduction in the cancer cells in the S phase with a significant induction of the tumor suppressor genes; cyclin-dependent kinase inhibitors Cip 1/p21, p38 MAPK (Mutagen Activated Protein Kinases) and Kip1/p27, suggesting that selenium possesses strong antiproliferative properties in regard to human prostate cancer (Venkateswaran et al. 2002; Jiang et al. 2002; Wang et al. 2002; Zeng et al. 2009; Connelly-Frost et al. 2006 and Rooprai et al. 2007). 10. Inhibition of DNA alterations by selenium that the mineral has also been shown to inhibit DNA binding of transcription factors AP-1 (Activator Protein 1, a protein that regulates gene expression in response to a variety of potent carcinogenesis such as some cytokines, growth factors, stress, bacterial and viral infections and in turn controls a number of cellular processes including differentiation, proliferation and apoptosis), NF-kβ (a protein complex that controls the transcription of DNA) and

DNA glycosylase (a family of enzymes which are involved in repair of DNA while stimulating the activity of thioredoxin reductase, TRX), a flavoprotein with an antioxidant effect which reduces redoxs proteins called thioredoxin (thus the enzyme inhibits toxic radical production and defends against cancer) and reducing p53, the tumor suppressor gene encoded by the TP53 gene (Seo, Kelley and Smith, 2002).

The STUDIES about the ASSOCIATION of SELENIUM with CANCER

- 3146 women with breast cancer, 416 breast cancer, mean age; 65 /1987-2009/smoking and alcohol included/highest quirtile as ≥27.7 μg/d Se intake (0.69,0.52-0.92) when compared with the lowest quartile as <20.6 μg/d Se intake (0.88,0.68-1.07), 95% CI, decreased the mortality of breast cancer (Harris et al. 2012).
- 803 men and women, 451 colorectal adenoma, 30-80 years of age/153-250 μg/L Se plasma concentration (0.6, 0.4-1.1, 95% CI) versus <140 μg/L Se plasma concentration (R:1.00, 95% CI) reduced the risk/smoking and alcohol adjusted (Connelly-Frost et al. 2006).
- 58279 men, 540 prostate carcinoma, 55-69 years of age/6.3 years of follow up/smoking adjusted, alcohol not)/ 0.663 μg toenail Se concentration (0.70, 0.48-1.01) versus 0.494 μg toenail Se concentration (1.05, 0.74-1.49), 95% CI, decreased the risk (van den Brandt et al. 2003)
- 120.852 men, 550 lung carcinoma, 69 years of age, 55-/3.3 years of follow up/smoking adjusted, alcohol not/>0.630 μg toenail Se concentration (0.40, 0.27-0.59) versus ≤0.530 μg toenail Se concentration(0.64, 0.47-0.89), 95% CI, decreased the risk of lung cancer (van den Brandt et al. 1993)
- 1103 men and women, 75 esophageal squamous cell carcinoma, 36 gastric cancer, mean age; 56.6/15 years of follow up/smoking and alcohol adjusted/>0.91 μmol/L serum Se concentration (0.35, 0.16-0.81) versus >0.77 μmol/L serum Se concentration (1.14, 0.63-2.04) decreased the risk of esophageal cancer and />0.91 μmol/L serum Se concentration (0.31, 0.11-0.87) versus >0.77 μmol/L serum Se concentration (0.62, 0.27-1.43), 95% CI, decreased the risk of gastric cardia cancer (Wei et al. 2004).
- 26975 men, 1329 prostate cancer, 55-74 years of age/alcohol and smoking adjusted/≥158 to 253 ng/mL serum selenium (0.84,

0.62-1.14) concentrations versus 50.5-126.8 ng/mL decreased the risk (Peters et al. 2007).

- 424 male, mean age 63.8/1989-1992/smoking and alcohol adjusted/200 mcg Se/d supplementation decreased the risk of skin cancer (1.5, 1.13-2.04), 95% CI, basal cell carcinoma (1.12, 0.96-1.31) and squamous cell cancer (1.88, 1.28-2.79) (Reid et al. 2008).
- 95 lung cancer, 113 laryngeal cancer, 2 healthy controls, 41-81 years of age/2009-2011/alcohol adjusted, smoking not/<60 μg/L versus ≥80 μg/L (0.10,0.03-0.34) decreased the risk of lung cancer and decreased the risk of laryngeal cancer(0.23, 0.09-0.56), 95%CI (Jaworska et al. 2013)
- 35242 men, 830 prostate cancers, 50-76 years of age/10 years of follow up/>50 μg/d Se supplementation did not decrease the risk (0.90, 0.62-1.3), 95% CI/ alcohol and smoking were not adjusted (Peters et al. 2008).

In spite of a limited number of studies that vitamin C has no anticarcinogenic effect, the vitamin has been claimed as having a significant anticarcinogenic potential with many ways against various cancers which have been proven by many studies. The vitamin donates an electron to redox-active transition metal ions such as cupric (Cu+2) or ferric (Fe+3) ions, reducing them to cuprous (Cu+) and ferrous (Fe2+) ions (Du et al. 2012). The reduced transition metal ions react with O_2, reducing it to superoxide radicals which in turn dismutate to form H_2O_2. Normal cells unlike cancer cells are less vulnerable to H_2O_2 whereas H_2O_2 significantly causes cancer cells to undergo apoptosis, pyknosis (thickening and degeneration of a cell in which the nucleus shrinks in size and the chromatin condenses to a solid mass) and necrosis (Chen et al. 2005). The sensitivity of tumor cells to H_2O_2 is not known but may be due to the weaker antioxidant defenses of tumor cells (Oberley 2002; Frei and Lawson 2008). Confirming this, treatment of Human Burkitt's lymphoma cells (JLP-119) with ascorbic acid in 0.3-20 mM concentrations killed the cancer cells as dependent on extracellular H_2O_2 and ascorbate radicals (Chen et al. 2005). Another anticarcinogenic effect of vitamin C stems from its effect on the enzyme, prolyl hydroxylase. Solid human tumors contain regions of very low oxygen concentrations called hypoxia. The uncontrolled proliferation of cancer cells at an increasing distance from blood vessels and thus, the poor limit of oxygen diffusion in these areas and also, the tortuous vasculature presented by tumors which results in an unstable blood flow are the initial factors that create the hypoxic media. Cancer cells tend to adapt themselves to hypoxia in order to survive by the activation of the transcription factor, hypoxia-inducible factor 1 (HIF-1) (Rankin and Giaccia, 2008). Basically, O_2 dependent hydroxylation of proline residues in HIF-1α is required which results in HIF-1α degradation. Prolyl hydroxylases are the enzymes belong to deoxygenase family that uses oxygen. Thus, under hypoxic conditions, the activity of prolyl hydroxylases that degrade HIF-1α decreases, resulting in a decreased

rate of HIF-1α degradation. On the other hand, the in vitro activity of prolyl hydoxylases is enhanced in the presence of ascorbate which results in the inhibition of HIF-1α activation by hypoxia (Page et al. 2008). Additionally, ascorbate plays the role of cofactors for prolyl hydroxylases since it maintains the iron centre of hydroxylases (Verrax and Calderon 2008). Briefly, vitamin C has been proven to have a significant anticarcinogenic effect by increasing the degradation rate of prolyl hydoxylase which are the essential enzymes for the degradation of hypoxia-inducible factor 1 (HIF-1) which adapts the tumor cells to the hypoxic conditions. Another attribute which causes anticarcinogenic potential of the vitamin is its inducing capacity on the detoxifying phase II enzymes (the group of enzymes that regulates the excretion of xenobiotics, the foreign bodies like pollutants and antibiotics, through urine or bile, after the transformation of xenobiotics into water soluble compounds with conjugation process by the phase I enzymes (cytochrome P450 enzymes in liver). The namely phase II detoxifying enzymes are NADPH: quinine reductase (one enzyme group to detoxify the ingested bacteria and fungi by forming superoxide and other free reactive oxygen species) and glutathione-S-transferase (the group of enzymes to detoxify xenobiotics by catalyzing the xenobiotic substrates with carbon, sulfur or nitrogen atoms, preventing their interaction with crucial cellular proteins and nucleic acids). Confirming this, anticarcinogenic effect of the vitamin, Wang and Higuchi (1995) cultured Colo205(colon cancer) cells in the presence or absence of ascorbic acid in concentrations of 10-10 to 10-5 M and noticed the increased activities of both enzymes, supporting a hypothesis that a high dietary consumption of vitamin C may confer partial protection against colorectal cancer by the induction of these specific detoxifying enzymes. Another anticarcinogenic effect of the vitamin is due to the induction of apoptosis via the modulation of Endoplasmic reticulum (ER) function through the vitamin. Several types of proapoptotic proteins in the outer mitochondrial wall which initiate apoptosis such as Bid and Bad (the members of proapoptotic protein family in mitochondria) initiate the apoptosis as in connection with the vitamin. Bid is a mediator in a TNF (Tumor Necrosis Factor, a cytokine involved in systemic inflammation, including fever and apoptotic cell death, inhibition of tumorigenesis)-receptor independent

apoptosis pathway followed by its dissociation from 14-3-3 protein. Vitamin C significantly increases the dissociation of Bad from protein 14-3-3 which initiates the apoptosis in cancer cells caused by Bad. Similarly, another proapoptotic protein, is also in connection with the vitamin and its expression was shown to increase by the treatment of vitamin C. The releasing of Ca_2+ ions from ER is an important for the dissociation of Bad from 14-3-3ß and this dissociation is increased by the vitamin. Briefly, the releasing of Ca_2+ ions from ER to HCT-8 (colon cancer cells) is the initial step in the apoptosis by the treatment of vitamin C. The induction of the apoptosis in human colon cancer cell line, HCT-8, through the calcium influx in ER by the vitamin, followed by the dissociation of another proapoptotic protein, Bad, by the same vitamin suggests that vitamin C may be a useful adjuvant for the treatment of colon cancer with chemotherapeutic drugs (Kim, Kang and Lee, 2012).

Photodynamic therapy is a form of phototherapy using nontoxic light-sensitive compounds that are exposed selectively to light and become toxic to targeted malignant tumor cells. Unfortunately, photodynamic therapy results in the formation of excessive amounts of reactive oxygen substances which may lead to irreversible tissue injury while killing tumor cells (Agostinis et al. 2011). On the other hand, during photodynamic therapy and other cancer treatments, ascorbic acid may play a central role in the defense of free radical-induced cellular damage (Padayatty et al. 2003). If the vitamin is used during cancer treatments like photodynamic therapy, may decrease the production rate of tumor killing reactive oxygen substances and thus be contraindicated in patients undergoing tumor treatment (Frank et al. 2006). The data mentioned here from these findings brings up that the effect of the vitamin and probably the other vitamins and minerals in antioxidant effect should be evaluated in two different parts. The anticarcinogenic effect of the vitamin before cancer formation and the tumor enhancing and contraindicated effect of the vitamin during cancer treatments. Briefly, the effect of the vitamin on cancer depends on the period of living. A significantly important anticarcinogenic effect of the vitamin can be claimed but only for healthy persons without cancer but not for the periods of cancer and its treatments.

Vitamin C has also been shown in vitro to have a significant anticarcinogenic potential against prostate cancer. This potential of the vitamin on prostate cancer stems from the effect of the vitamin on two important prostate cancer indicators; kallikrein 2, a protein that is encoded in humans by the KLK-2 gene and associated with prostatic tissue and Prostate Specific Antigen (PSA), also known as gamma-seminoprotein as kallikrein-3 which is a glycoprotein enzyme and secreted by the epithelial cells of the prostate gland. The addition of the vitamin into Los Angeles prostate (LAPC-4) human cancer cells was shown to decrease both of the pancreatic cancer indicators, similar to the phenomenon observed when cells were treated with hydrogen peroxide (Wang, Abreu-Delgado and Young, 2003). Similar to KLK-2 and PSA, other chronic inflammatory agents predispose susceptible cells to neoplastic transformation which may induce DNA mutations in cells via oxidative/nitrosative stress and hence tumor formation. The ratio of the inflammatory agents and the generation of free radicals and oxidative intermediates, when exceed the immune system's ability to neutralize and eliminate them, increases the risk of DNA mutation and tumor formation. This is a process which continues by the production of free radicals and soluble inflammatory mediators such as metabolites of arachidonic acid, cytokines and chemokines which act by producing further reactive species that may induce DNA mutation and tumor formation. Therefore, high oxidation rate and oxidative stress with its inflammatory agents, cytokines, chemokines such as KLK-2, PSA and free radicals often predisposes the cell to DNA mutation and hence tumor formation. This predisposition to cancer caused by oxidation free radicals and inflammatory agents make the antioxidation by antioxidants very crucial (Federico et al. 2007) The levels, the daily consumption rate of antioxidants and the ratio of them including ascorbic acid, and others; vitamins A, B complex,, D, E, K, antioxidant minerals; Mg, Ca, Se and Zna and additionally antioxidant enzymes (lipooxygenase, cyclooxygenase and phospholipid hydroperoxide glutathione-peroxidase, hydroperoxides and lipoperoxides) to the free radicals, prooxidants and inflammatory agents, may be strong determinants for the progress of cancer and cancer prevention. Briefly, the vitamin can decrease the risk of cancer with its antioxidant potential.

As the data clearly mentioned above, the effect of inflammatory free radicals, cytokines and chemokines which produce further reactive species and tumor formation often form an inflammation during the disease. While these inflammatory agents cause DNA mutation and subsequently tumor formation, the tumor cells often cause the higher production rates of cytokines and chemokines by immune system to kill them which may result in further cytokines and chemokines. Thus, the two phases; inflammation and cancer may often appear as the results of each other and feed and induce each other. The close relation between inflammation and cancer indicates to the importance of the inhibition of inflammation during cancer (Mikirova et al. 2012). The vitamin has also been shown to decrease inflammatory tumor markers like PSA, the protein produced by cells of the prostate gland which is often elevated in men with prostate cancer, CEA, the carcinoembryonic antigen that appears in the blood of some people who have certain kinds of cancers especially colon and rectal cancers, CA 27.29 and CA15-3, the antigens which are used to predict early recurrence of breast cancer in women while reducing another inflammatory agent, C-reactive protein, the protein in blood, the levels of which rise in response to inflammation, IL(Interleukin)-1α, the protein which increases by inflammatory agents, infections, microbial endotoxins, IL-2, the protein which increases to regulate the activities of white blood cells (leukocytes and lymphocytes) for immunity against inflammatory agents, IL-8, a chemokine, a kind of small cytokine or signaling protein secreted by cells, produced by macrophages which directs and migrates them the site of infection, Tumor Necrosis Factor (TNF or other names; cachexin, cachectin, tumor necrosis factor α), a cytokine produced by activated macrophages against inflammation, chemokine eotaxin, CCL11, eosinophil protein which induce chemotaxis (the movements of cells) of eosinophiles during inflammation and CRP, C-Reactive Protein, the protein produced by the liver in case of inflammation (Mikirova et al. 2012). Confirming the anticarcinogenic potential of the vitamin due to its anti-inflammatory effect, 500-1000 mg vitamin C daily supplementation has been claimed to augment glutathione in human lymhocystes which results in the inhibition of lipid peroxidation, the production rate of free radicals from lipid peroxidation (Lenton et al. 2003) and a significant decrease

in the production of 8-Oxoguanine. 8-Oxoguanine is one of the most common destroyers to DNA which can result in a mismatched pairing with Adenine resulting in Guanine to Timin and Adenonine to Citosin substitutions in the genome resulting with the DNA mutation and tumor formation (Padmore et al. 1998).

Another anticancerogenic effect of the vitamin is due to its ability to inhibit nitrosation, a process of converting organic compaunds into nitroso derivatives and the production of potentially mutagenic N-nitroso compounds in the stomach via to nitrites in dietary nitrogen compounds. Although ascorbic acid disappears rapidly in gastric juices of patients with hypochlorhydria, high dose vitamin C supplements and fruit juices rich in this vitamin may inhibit the gastric N-nitrosation in stomach of healthy patients without hypochlorhydria (O'toole and Lombard 1996). On the other hand, when the close association between dietary N-nitroso compounds and increased risk of gastrointestinal cancers (1.13, 1.00-1.28, 95% CI) (Loh et al. 2011; Keszei et al. 2013) especially in industrialized countries heavily rely on fast food rich in N-nitroso compounds, this protection by the vitamin may have an uppermost importance especially to lower the risk of gastrointestinal cancers in such countries where fast food nutrition style is widespread.

Limitations for the determination of anticancerogenic potential of vitamin C and other food nutrients

One of the important studies carried out to determine the effect of vitamin C on cancer is very significant since it finds the anticarcinogenic effect of the vitamin on prostate cancer with patients who do not use alcohol, but the same authors did not find any association between prostate cancer and the vitamin for the patients who drink alcohol regularly. It clearly shows that regular intake of alcohol is one of the crucial factors that may change the prospect of vitamin's anticarcinogenic potential. On the other hand, a measurable amount of cohort studies to determine the effect of dietary nutrients and their supplements on cancer have been performed without adjusting alcohol intake. Another factor that determines the anticarcinogenic potential of the vitamin is the time period which the vitamin or its supplement is taken into the body. Confirming this, 240-3220 mg/d vitamin C supplementation of women with breast cancer in premenopausal period and 440-3850 mg/d vitamin C supplementation of women with breast cancer in postmenopausal period decreased the risk of breast cancer after 10 years or longer supplementation period of the vitamin but less than 10 years of supplementation, did not make and change. Another failure that limits the scientific sensitivity of such cohorts which analyze the anticarcinogenic potential of vitamin C or any other food nutrient is the use of different ambiguous measurements like % rather than using clear and definite measurements like 'mg' or 'IU'. It is often impossible to understand the real daily vitamin C amounts from '%' values. Like in the study of Jacobs et al. (2002), % of daily vitamin C is ambiguous since it can only give a comparison among the different batchs of cohorts to each other but can not give any idea about the amount of the vitamin. In such cohorts, we strongly need definite and clear amounts that show the daily dose intakes which can only be expressed by 'mg', 'g' or 'IU'. On the other hand, these heterogenic measurements are used in cohorts to make their comparisons and analysis in meta analyze studies. In case

of 'mg' or 'g' or 'IU' measurement uses, all cohorts in the meta analysis can be compared but it is impossible to make the same comparison if different cohorts use different measurements like 'mg', 'g' and 'IU'. A comparison between two studies, one using 'mg' and the other using '%' can not be possible which significantly restricts the sensitivity of meta analysis based on cohort studies. Another confirmatory example belongs to the same editor in chief with his two different studies (Jacobs et al. 2001 and Jacobs et al. 2002). The same author with his team finds out a significant protection of higher % daily supplement intakes of vitamin C in a large cohort using 711891 men and women with adjusting smoking but without adjusting alcohol. One year later, the same author with his team does not find any significant effect of the same vitamin supplement use ≥15 times per month in another large cohort using 991552 men and women with adjusting both smoking and alcohol. Both % daily vitamin supplement intakes and the vitamin supplement uses per month do not present the exact amount of the vitamin which also lack the comparison of both different measurements and reach an evaluation. For example, the vitamin C supplement intake ≥ 15 times per month may be too insufficient if the amount of the vitamin per tablet is too small and similarly the % vitamin C supplement use may be too low if the amounts of the vitamin taken into the body in the highest % quartile are too small. Another example for the studies which analyze the relation between cancer and food by using ambiguous terms belongs to Hara et al. (2011). The authors observed no association between the supplementation of vitamin C and total cancer in men but they also did not give any information about the supplement elemental vitamin C amount. Similar to all the mentioned examples above one other author with another team compared the regular vitamin C users and non users and determined the anticarcinogenic potential of the vitamin against skin cancer (Jacobs et al. 2002), but again by using vague descriptions like vitamin C user or non user. In these descriptions, the elemental vitamin C intakes into body by the means of supplements are in question which limits the scientific evaluation of the anticarcinogenic potential of the vitamin.

Another factor that limits the sensitivity of such cohorts to determine the effect of food nutrients including vitamin C is the nutritious status

of subjects. For example, Berndt et al. (2005) did not determine any significant association between vitamin C and prostate cancer in their study, but also added that the subjects in their study were all well-nourished. Here, the question of 'is the anticarcinogenic potential of the vitamin due to the vitamin itself or any other nutrient since the subject in the study is well nourished?' makes a barrier for us to believe and make a completely scientific evaluation of the findings of such cohorts. Another barrier in showing the anticarcinogenic potential of the vitamin (or any other nutrient) is the extension of the follow up. It is obvious that the longer the years of follow up is, the higher the sensitivit the cohort will have. Confirming this, Botterweck, van den Brandt and Goldbohm (2000) kept the follow up period as 6.3 years that was sufficient enough to catch any abnormal change on the effect of vitamin C on gastric carcinoma. Although they found an inverse association between the cancer and vitamin C for the first and the second years, they could not find the same effect after two years which might be due to a possible decrease in immunity of the subjects or increase of allergens or any similar harmful environmental substances or resistivity of cancer cells against vitamin by the time. Another factor that limits the sensitivity of such studies which analyze the effect of the vitamin on cancer is the use of the parameter. If any parameter besides the vitamin or any other food constituent studied is taken into consideration as combined with the vitamin, naturally, the sensitivity of the study to determine the effect of the vitamin on cancer decreases, like in the study belong to (Eichholzer et al. 2000). The authors analyzed the combined effect of both vitamin C and cholesterol on various cancers and did not find any association between vitamin C in the patients with high cholesterol and cancer. Unfortunately, another parameter like cholesterol level in this one might have affected the anticarcinogenic potential of the vitamin and may decrease the sensitivity of meta analysis about food and cancer relations.

Vitamin C, ascorbic asid (ascorbate)'s one initial anti-cancer effect is via the ROS production, especially H_2O_2, on human lymphoma cells, the cancer cells with a highest sensitivity to ascorbate, with its less than 4 mM- a concentration easily achievable i.v. (Chen et al. 2005).

The vitamin appears as a symbol which clearly shows most that the

anti-cancer effect of a vitamin or a flavonoid depends on some important factors which requires an evaluation about the anti-cancer status of the substance that may be very contraversial and not so easy. The first three factors that affect the anti-cancer potential of the vitamin and may be a rationale for the controversial claims as related to the anti-cancer effect of it are; the type of the cancer, the dose of the vitamin and the company of the other vitamins and/or flavonoids. The vitamin with 0.25-1 mM/24h causes 50 % decrease in survival of human myeloid leukemia cell line, HL-60 (Park 2013) while normal cells are insensitive to 20 mM ascorbate (Chen et al. 2005).

The i.v slow drip infusion in saline solution to the patients with prostate, breast, bladder, pancreatic, lung, thyroid cancer or skin cancer, as in high doses (7.5g-50g) decreases all tumor markers, PSA, CEA, CA27.29, CA15-3 and C-reactive protein in all cancers, decreasing the survival times of the mentioned cancers (Mikirova et al. 2012).

Of the 46 studies about the high dose vitamin C and cancer; 33 found statistically significant protection in the review of Block (1991) that all the studies in this review had used above 5000 mg/d (the equivalent of 100 oranges). In the second review of the same author, in the same year the high doses a ≥5000mg/d of ascorbic acid was claimed to have statistically significant protective effects on the cancers of oesophagus, oral cavity, stomach and pancreas, based on 90 epidemiologic studies. Confirming this, 5-30 g of vitamin C causes six times longer survival time for cancer patients as compared with the patients on 4g (Murat and Morishige 1981).

The previous studies carried out by Cameron and Pauling (1976) and (1978) and Jaffey (1982) which similarly confirmed the statistically important anti-cancer potential of high-dose ascorbic acid administrations ≥5-30 g were discredited by Creagan et al. (1979). Then, it was realized that the disaggrement of Creagan et al. (1979) was due to the difference in dose and administration interval. The previous studies of Cameron and Pauling and the 46 studies in the reviews of Block (1991) had administered vitamin C in high dose everyday and continued more than 75 days whereas Creagan et al. (1979) had stopped the vitamin administrations after an average of 75 days.

In the meta-analysis carried out by Harris et al. (2014) which

includes 10 studies, an increase in vitamin C intake of 100 mg/d was found to be associated with a reduction in all causes of death and higher increases were associated with a 20 % reduced risk in all causes of death, compared to lower intakes. Similarly, the increase in vitamin C intake of 100 mg/d reduced the risk of death 23 % from breast cancer. But, the amounts of supplemented vitamin C in all studies of the meta-analysis ranged from 400 mg/d to 1000 mg/d, with 1000 mg/d being the most common dosage.

Unexpectedly, there seem a very limited number of studies about the anti-cancer effect of the vitamin in spite of many controversial and conflicted discussions. This means clearly that the evaluations related to the anti-cancer potential of the vitamin is based on a very limited amount of study and one of these studies is also waiting to be repeated in human subjects. The study carried out by Chen et al. (2008) administered extremely high dose, 4 g ascorbate/kg, in mice but as in single dose or two times dose administrations and the authors claim to reach >0.2 mM ascorbate concentrations in plasma only by circumventing oral tight control with parenteral administration. The findings may be important since hyrogen peroxide, produced by the vitamin and ascorbate radicals, two of which are the initial prooxidant radicals of the vitamin to kill tumors, here were only found in interstitial fluids of tumors but not in blood. The single and two times administrations in the extremly high dose of the vitamin could significantly decrase the growth rate of ovarian, panaeatic and glioblatoma tumors in mice an a result of significantly increased H_2O_2 concentrations in interstitial fluids of tumors. Though the side effects, like iron overload, glucose-6- phosphate dehydrogenase deficiency and oxalate neghropathy was claimed, it is urgently needed to administer such high doses of the vitamin in cancer patients as in single or two-time administration and determine the effects of the anti-cancer and side effects of the extremly high dose administrations of the vitamin on various cancers.

Although, the vitamin is commonly regarded as an antioxidant, in the existence of organic substrates, it may act as a prooxidant. The oxidation of organic substrates by iron (II) and hydrogen peroxide produced by the vitamin, other words, the Fenton reaction, may be the origin of the anti-cancer of the vitamin via H_2O_2 and other prooxidant

radicals. Iron (II) is oxidized by hydrogen peroxide to iron (III), forming a hydroxyl radical and a hydroxide ion in the reaction. Iron (III) is then reduced back to iron (II) by another molecule of hydrogen peroxide, forming a peroxide radical and a proton. Ultimately, two different oxygen-radical species, H+ and OH- form as a by product through the disproportionation of hydrogen peroxide. Once, the two requirements, the biological reduction agent, vitamin C (or some other antioxidants) and iron existence, the production of OH- (hydroxyl radical) which is produced from H_2O_2 in mitochondria by the vitamin and which is highly toxic, with other prooxidants in the same reaction, has long been regarded as a major reason for the aging process and a variety of diseases such as cancer, neurodegenerative diseases, atherosderosis, etc. (Prousek 2007).

The inhibitory effect of the vitamin on cancer by using H_2O_2 and other prooxidant radicals formed during Fenton reaction by the vitamin has been confirmed in various studies (Gottlieb 1999; Ohtani et al. 2007; Zou et al. 2006).

On the other hand, the Fenton prooxidants and H_2O_2 of vitamin C, especially during the single or two times high dose administrations, may be in synergism with the anti-cancer drugs which target tumors similarly by using their ROS production, the anti-cancer drugs like; sunitinib, sorafenib, tetrandrine, cisplatin, bortezomib, vorinostat, MG-132, metformin, thopsigargin, tunicamycin, 17AAG, DBeQ, ritonavir and brefeldin A. But, there is no any study to highlight this synergism between the mentioned drugs and the vitamin to kill tumors via the H_2O_2, Fenton prooxidants and other ROS and neither in smokers or in patients who consume cooked meat and meat products regularly (which may lead to extremely high amounts of ROS, inducing hypoxia in such target groups who supply beta caroten in the same periods). But in other patients, the consumptions of high dose vitamin C administrations as combined with beta carotene and beta carotene and vitamin C rich foods like; banana, broccoli, (fresh) cabbage, grapefruit, spinach(fresh), tomato, lettuce (Vanderslice and Higgs 1991) and cifrose fruits; orange and lemon (Marti et el. 2009), and the mentioned drugs may enhance the anti-cancer effect of these drugs and vitamins since all of them target tumors by ROS. The combined administration of each of these

drugs with high dose vitamin C and/or beta carotene and its effect on cancer via the synergism of ROS, H_2O_2 and Fenton prooxidants need urgently to be studied in a very near future (provided that the possible side effects due to extremely high dose vitamin C administrations, iron overlood, glucose-6-phosphate dehydrogenase deficiency and oxalate nephropathy should be checked). The finding of these studies in a very new future may gain a new and strong anti-cancer status to the vitamin, the drugs and beta carotene.

Though, the vitamin with its H_2O and Fenton prooxidants may enhance the anti-cancer drugs which target tumors via the ROS production, it attenuates the activity of caspases, the enzymes that permeabilize the mitochondrial membrane and results in the influx of ROS out of the membrane. Therefore, neither the high dose administrations of the vitamin nor the vitamin C consumptions of rich foods; banana, broccoli, cabbage, grapefruit, spinach, tomato, lettuce, orange, lemon, other citrus fruits and green leafy during the treatments by caspase-inducing anti-cancer drugs like costunolide, mitomyecin C, garcinol, valinomycin, piceatannol, kinetin riboside, lipase inhibitor, THL(tetrahydrolipstatin), imiquimod, SC560, romidepsin, ouabain, digoxin, proscillaridin A, borrelidin, sanguinarine, MT-21, Ionidamine, K858, saikosaponin A, CIL-102 and prodigiosin, may be contraindicated since the vitamin attenuates caspase activity opposite to the mentioned drugs. Although brefeldin A, cisplatin and boritezomib induce ROS and thus may enhance the anti-cancer drugs which target tumors by producing ROS, they activate caspase activity and may be contraindicated if administered as combined with high dose administrations of vitamin C which attenuates caspase activity. Please note that, these drugs may also be contraindicated with the heavy smokers with or without beta carotene suplementation (and/or beta carotene rich food consumption including carrot, amaranth, guava, mango, papaya, strawberry, red chili, orange, suparapple, cucumber, green chili, minr and french bean) and heavy cooked meat consumption because of the risk of extremely ROS production which may lead to hypoxia and damage the healthy cells together with the cancerous one.

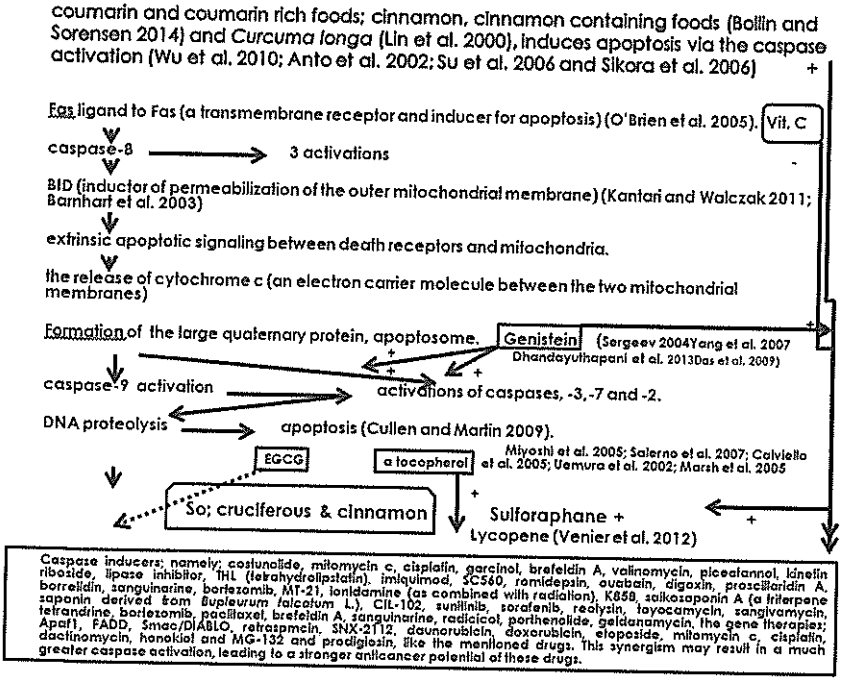


FIGURE 12

One of the anti-cancer effects of the vitamin may be its inhibitory effect on COX-2, the enzyme which is responsible for the inflammatory hormones while inhibiting the antiapoptotic hormone, IGF, where actions are mediated via the PI-3 kinases, the enzymes which are involved in cell growth and survival (Lee et al. 2008).

Although Candelario-Jalil et al.(2006) did not observe any synergism between the vitamin and the COX inhibitors, and indomethacin (which may be due to the weak inhibitory effects of the two drugs on COX activity), the possible synergisms of the vitamin with other COX inhibitors like sunitinib, celecoxib, magnolol, honokiol, eugenol, bis-eugenol, tetrandrine, 17AAG, raloxifene, rofecoxib, nafroxen, dexamethasone, hydrocortisone, triamcinolone acetonide, methyl prednisolone, beclomethasone diproprionate, need urgent studies to highlight these synergisms. The findings of the needed studies may gain a new synergism status of the mentioned drugs, enhancing their anti-cancer effects via the inhibition of COX and IGF.

The vitamin also attenuates ERK and controls ERK signaling and inactivates ERK 1-2, the intracellular protein serine/threonine kinases which act anti- apoptotic (Park et al. 2010; Ulrich-Merzenich et al. 2007).

Therefore, the high dose vitamin C administrations may enhance the anti-cancer potential of the drugs which kill tumors by inhibiting ERK signaling, namely; vorinostat, ritonavir, radicicol, tamoxifen, geldanamycin, lapatinib, fulvestrant, PD98059, UO126, honokiol, SNW212 while sulforaphane supplements and sulforaphane rich foods; white cabbage, Brussels sprouts, radish, mustard, broccoli, red cabbage, cauliflower, Chinese kale and turnip should be avoided since the bioflavonoid induces ERK activity unlike beta carotene supls and beta carotene rich foods, carrot, amaranth, guava, mango, orange, papaya, strawberry, supar apple, cabbage, green chili, cucumber, spinach, tomato, lettuce, mint, red chili and French bean.

That Vitamin C inhibits the estrogen activation of ERalpha, (in spite of a very limited number of studies, except the one carried out by Almeida et al. 2015), may indicate to a probability to a better prognose in case of combination of vitamin C suplements, vitamin C rich foods and ERalpha inhibitors; nafoxidine, hexestrol, C1618 and dienestrols since the mentioned drugs similarly inhibit ERalpha activation during cancer treatments.

Similar to resveratrol, the vitamin decreases the expression of prostate-specific antigen (androgen receptor) (Wang et al. 2003.). Thus, the combined consumption of resveratrol rich foods; peanuts, grapes, blueberries, vitamin C rich foods; banana, broccoli, fresh cabbage, grapefruit, fresh spinach, tomato, lettuce, citrose fruits-orange lemon and grean leafy vegetables, with or without resveratrol and vitamin C supplements, (according to the directions of the physician) and androgen receptor antagonist, Flutamide, may be useful. Though, there is no any study which shows the synergism to inhibit cancer between the rich consumption of resveratrol and vitamin C rich foods and Flutamide, the involvement of such foods during the treatments with androgen receptor antagonists may have a chance for a better prognosis since vitamin C and resveratrol are the androgen receptor antagonists, similarly.

FOXO3, the gene and a transcription factor which triggers apoptosis

through the upregulation of other apoptotic genes like Bim and PUMA, is induced by ascorbic acid just followed by the activation of the antioxidant system, thioredoxin (Li et al. 2009; Parody et al. 2014). Therefore, the anti-cancer potential of the drugs which kill tumors via the induction of FOXO3, namely; metformin, doxorubicin, nipradilol, timolol, melatonin, withaferin A, bortezomib, rorinostat, tunicamycin, paclitaxel, geldanamycin, A205363, cisplatin and 5-aza-2-deoxycytidine, may enhance if they are administeed as combined with vitamin C rich foods; banana, broccoli, fresh cabbage, fresh spinach, tomato, lettuce, citrose fruits, grean leafy, besides beta carotene rich foods; carrot, amaranth, guava, mango, papaya, sugarapple, strawberry, cucumber, green chili, red chili, mint, french bean and resveratrol rich foods; peanuts, grapes and blueberries, since all there foods and the vitamin C ones induce FOXO3, similar to the mentioned drugs.

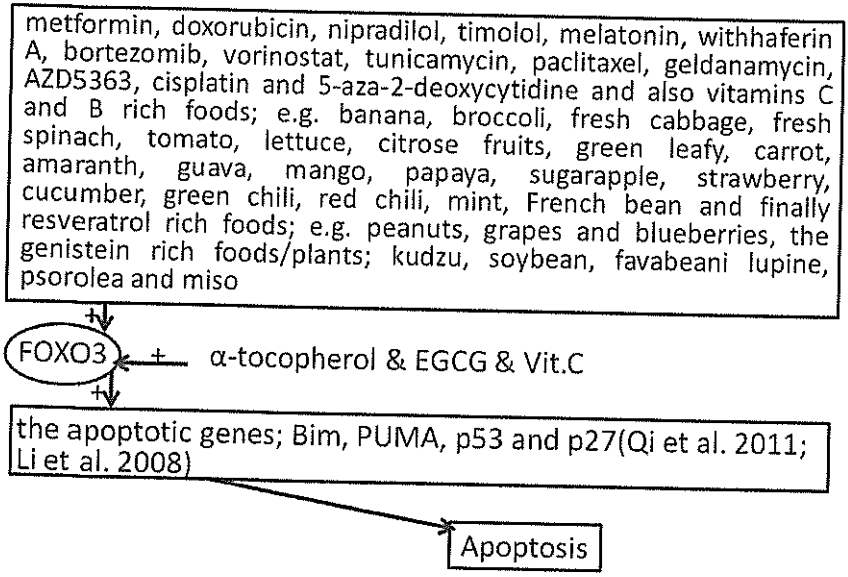


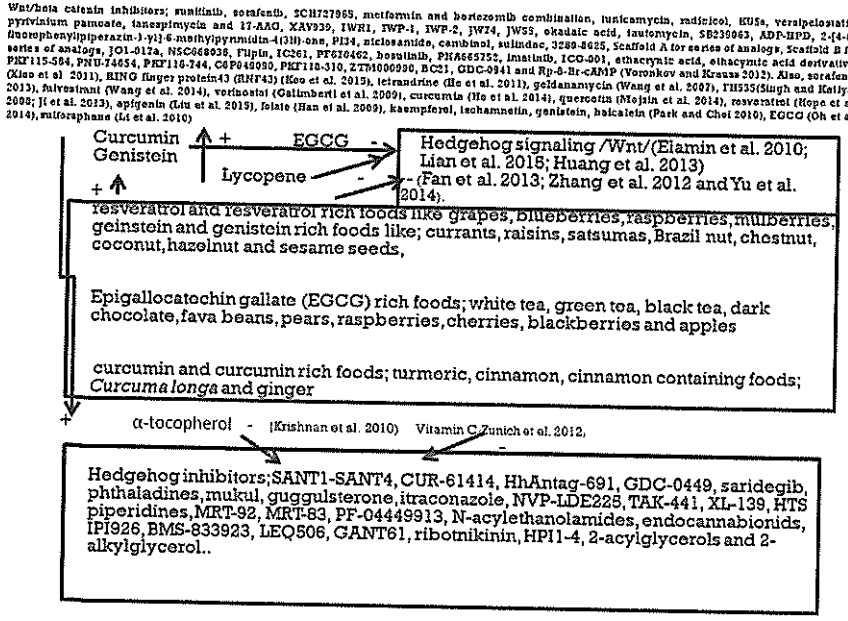
FIGURE 13

The proteasome, namely 20S proteasome, is an essential component of the ATP-dependent proteolytic pathway and is responsible for the degradation of most cellular proteins. Bortezomib inhibits 20S proteasome activity which forms one of the anti-cancer effects the

drug, but this inhibition is blocked by vitamin C (Perrone et al. 2009). Therefore, either vitamin C, supplements or vitamin C rich foods should be avoided, during the treatments with bortezomib.

The only study, currently indicates the the relation between the activity of Akt, serine/threonine-specific protein kinase which plays a key role in cellular processes, and vitamin C, claims that the vitamin has not any inhibitory or stimulatory effect on the enzyme (Choi et al. 2010). Therefore, without any positive or negative expectations, vitamin C rich foods may better be avoided during the treatments with the drugs which inhibit Akt, namely; LY29002, SF-1126, NVP-BEZ235, XL147, XL765, ISC-4, GSK690693, MK-2206, fused pyrimides, PIP3, GDC-0941, celecoxib, UCN-01, BX-795, BX-912, BX-320, CCT128930, GDC-0038, perifosine, GSK-2141795, GSK-2110183, Ipatasertib, Afuresertib, AT13148, PF-04691502, A47867 and Triciribine, until the relation of the vitamin and Akt is highlighted with more studies.

In spite of the various anti-cancerogen effects of the vitamin, it potentiates Hedgehog (HH) signaling, the signaling which transmits information to embryonic cells for the cell development and survival (Zunich et el. 2012) and thus the vitamin C supplements and vitamin C rich foods should be avoided during the treatments with the drugs; SANTI-SANT4, CUR-61414, HhAntag-691, GDC-0449, guggulstesone, Saridegib, phthaladines (e.g. LY2940680, NVP-LEQ506), Itracanazole, NVP-LED225, TAK-441, XL-139, HTS piperidines, MRT-92, MRT-83, PF -04449913, N-acylethanolamides, 2-acylglycerols and 2-alkylglycerol, the drugs which inhibit Hh signaling.



FIIGURE 14

GRP78, the central regulator of endoplasmic reticulum (ER) and a chaperon, controls ER with its protein folding capacity. Vitamin C significantly attenuates cadmium-induced upregulation of the chaperon (Ji et al. 2012). Thus, the anti-cancer effects of the drugs which inhibits the chaperon like vitamin C, namely; sunitinib, sorafenib, SCH727965, metformin and bortezomid combination, tunicamycin, radicicol, KUSs, versipelostatin, pyrivinium pamoate, tanespimycin, 17-AAG, may enhance if they are administered as combined with the food consumption rich in vitamin C.

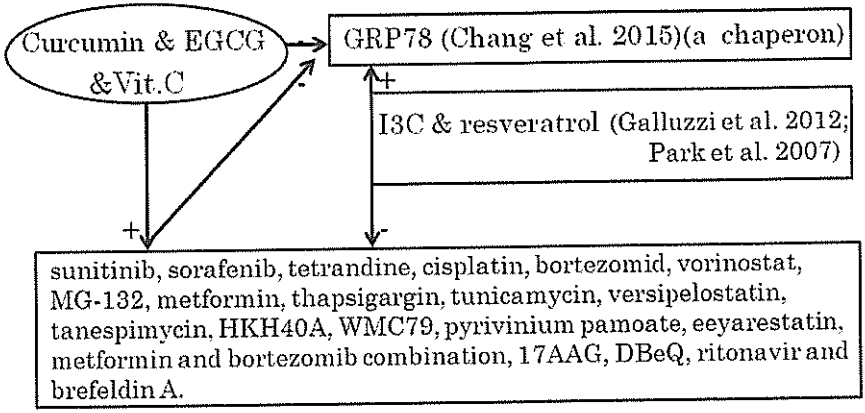


FIGURE 15

The vitamin also causes loss of G-6-PD (glycose-6-phosphate dehydrogenane) and inhibition of G-6-PD activity (Udomratn et al. 1977). Thus, the drugs which induce apoptosis by inhibiting G-6-PD, namely; steroid DHEA1, DHEA, chloroquine, flutamide, and rasburicase may show greater anti-cancer effect if they are administered during the food consumption rich in vitamin C, opposite to the resveratrol rich foods (e.g. peanuts, blueberries, grapes, though these foods are also rich in vitamin C, they may be contraindicated with the mentioned drugs because of their resveratrol contents!). But, note that, vitamin C supplements and heavy food consumptions rich in vitamin C, though they may enhance the apoptotic effects of the mentioned drugs with their synergy to inhibit G-6-PD and induce apoptosis, this combination may worsen the prognosis in G-6-PD deficient anemic patients since the vitamin inhibits G-6-PD activity and causes the loss of the enzyme in erythrocytes (Tang et al. 2015).

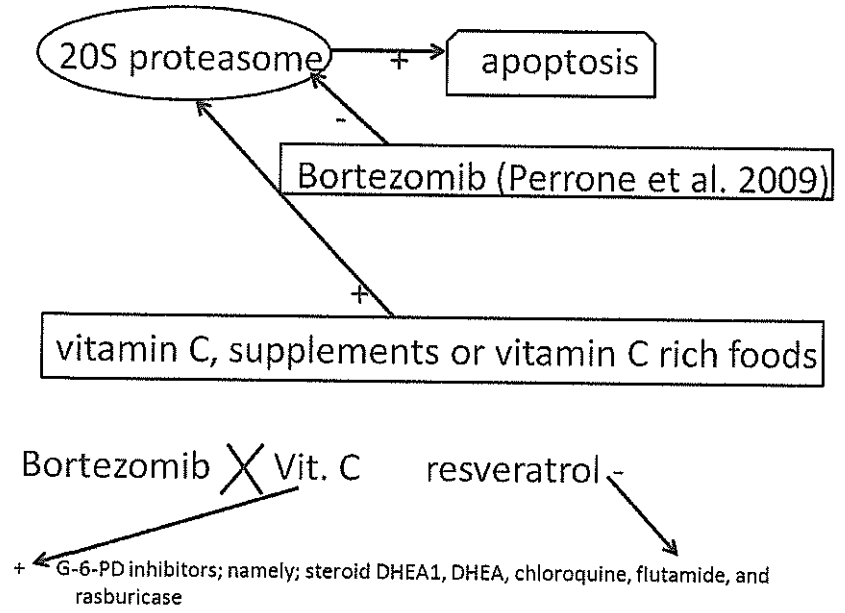


FIGURE 16

The protein which controls the production of most phase II enzymes to increase the solutility of the toxic and cancerogen compounds and reduce their toxicity, Nrf2, is activated by vitamin C (Wagner et al 2010; Kim et al. 2015). For this reason, involvement of vitamin C supplements and/or vitamin C rich foods; banana, broccoli, cabbage, grapefruit, spinach, tomato, lettuce, orange, citrus fruits (e.g. orange, lemon) and green leafy vegetables, but also sulforaphane rich foods like, white cabbage, broccoli, red cabbage, cauliflower, Brussels sprouts, radish, mustard, turnip and Chinese kale, curcumin and curcumin rich foods; cinnamon, cinnamon containing foods and curcuma longa, epigallocatechin-3-gallate (e.g black and green tea), resveratrol and resveratrol rich foods; grapes, blueberries and peanuts, cafestol and kahweol (coffee and tea), garlic organosulfur compounds, lycopene (red pepper, tomato and tomato products, strawberry), carnosol (rosemary) (Roma-Vaquero et al. 2014), oltipraz (the organosulfur in cruciferous vegetables), phenethylisothiocyanate (PEITC) (in Brassicaceae family vegetables), alfa-tocopherol and alfa-tocopherol rich foods; cauliflower,

potato, leek, onion, parsley, cucumber, codfish, cottage cheese and coconut, coumarin and coumarin rich foods (cinnamon, cinnamon containing foods; curcuma longa, billbery, green plants, cloudberry, green tea), 13C rich foods (Brussels sprouts, cabbage, cauliflower, collard greens, kale, kohlrabi, mustard, rutabaga, turnips, bok choy, Chinese cabbage), Beta-carotene rich foods (chard, cilantro, collards, corn, cabbage, carrot, Brussel sprouts, broccili, green beans, asparagas, apple, banana, pear, avocado, grape leave, lettuce, mango, melon, okra, onion, orange, red pepper, Japanese persimmons, raspberries, winter squash and tomato) as combined in a diet for cancer nutrition, may be useful in cancer prevention and the protection by inducing Nrf2 via the activation of glutathione S-transferase (GST), since all there nutriets including vitamin C increase the solubility of the toxic and cancerogen compounds and thus elemination of them out of body, inducing Nrf2.

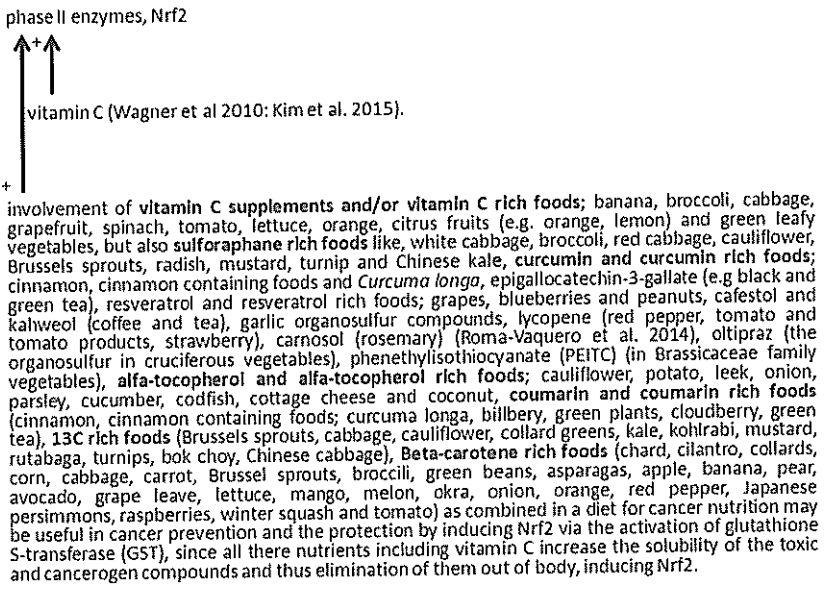


FIGURE 17

Vitamin C also inhibits Hem oxygenous-1 (HO-1), the enzyme which produces teratogens; carbone monoxide, biliverdin and free iron (Elbekai et al. 2007; Berger et al. 2000; Jin et al. 2013 and Zhao et al.

2014). The inhibition of the enzyme by vitamin C, may be another pathway for the anti-cancer effect of the vitamin and its cancer prevention. Accordingly, the treatments which target (HO-1) inhibition; tin (IV) protoporphyrin IX dichloride (SnPP), zinc (11) protoporphyrin IX (ZnPP), zinc(11) deuteroporphyrin IX-2, 4-bisethyleneglycol, imidazole-based compounds (8, 9, 10R, 10S, 11, 12,13,3), caveolin-1, calcineurin, siRNA, metformin, tin-mesoporphyrin, ZnMP(zinc mesoporphyrin), CrMP(crom mesoporphyrin), SnPP(tin-protoporphyrin), ZnPP(zinc protoporphyrin), PEG-ZnPP(pegylated zinc protoporphyrin), OB-24 ([2-(4-bromophenyl) ethyl]-2-[(1H-imidazol-1-yl) methyl]-1, 3-dioxolone hydrochloride), may show stronger anti-cancer effect if they are administered as combined with vitamin C rich foods; banana, broccoli, cabbage, grapefruit, spinach, tomato, lettuce, orange, lemon, green leafy, since all these drugs and the vitamin inhibit (HO-1) and hence may prevent the further production of teratogens. But, enterolactone (flaxseed, sunflower, sesame, pumpkin seeds), capsaicin, dihydrocapsaicin (hot pepper and hot pepper containing foods), matairesinol (whole grains), lariciresinol (Brassica vegetables; Brussel sprouts and broccoli), pinoresinol (sesame and Brassica vegetables, esculetin, coumarin and coumarin containing foods (e.g. cinnamon, cinnamon containing foods, *Curcuma langa*) and sulforaphane and sulforaphane containing foods (e.g. white cabbage, broccoli, red cabbage, cauliflower, Brussels sprout, radish, mustard, turnip and Chinese kale) should be avoided during the treatments with the mentioned drugs and vitamin C and vitamin C rich foods, since these foods and nutrients may decrease the anti-cancer potential of these drugs and the vitamin by inducing (HO-1) activity.

Though, the enzyme p38, a mitogen-activated protein kinase, has been shown to induce apoptosis in some cells, it may also prevent apoptosis in others, depending on the stimuli and cellular context (Bradham and McClay 2006). It can inhibit cell growth by decreasing the expression of cyclin D, a protein to regulate cell cycle progression. Thus, the activation of the enzyme has currently been appeared on a novel target in cancer treatments.The vitamin suppresses p38 activity (Kim et al. 2008 and Bowie and O'Neill 2000) which should be considered carefully in the treatments. That the vitamin suppresses p38 activity (Kim et al. 2008 and Bowie and O'Neill 2000) should be considered

carefully in the treatments with cisplatin, transplatin, platinum (IV) chloride, brefeldin A, thapsigargin, tunicamycin, tamoxifen, betulinic acid, honokiol, bortezomib, 4-phenyl-3-butenoic acid (PBA), vorinostat, geldanamycin, raloxifen, paclitaxel and panaxydol (the roots of *Panax ginseng*), the drugs, all of which activates p38, since vitamin C and vitamin C rich food consumptions during the treatments with the mentioned drugs suppress p38, opposite to the drugs and thus may decrease their anti-cancer potential. On the other hand, under some conditions (that these conditions, either the stimuli, the cellular context or the others, still remain to be highlighted) in which p38 may lead to apoptosis, limited number of p38 inhibitors; doramapimod (BIRB796), VX-745, VX-702, AMG-548, Scio-323, Scio-469 and pamapimod (RO4402257) have currently been administered (Genovese 2009), but a possible synergism of vitamin C with these molecules to yield a greater level of apoptosis is unknown and needs studies to be performed.

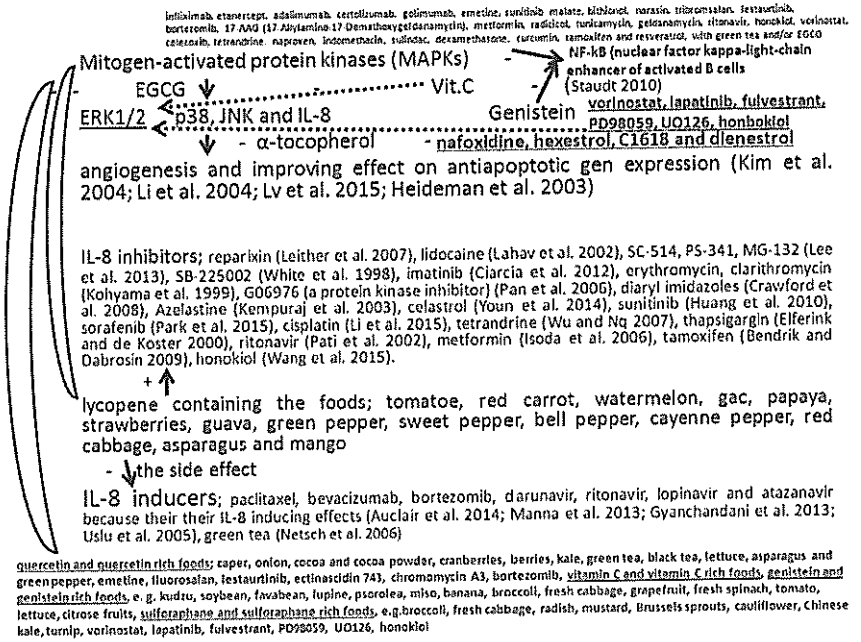


FIGURE 18

The STUDIES about the ASSOCIATION of VITAMIN C and CANCER

- 58.279 men, 642 prostate cancer, 55-69 years of age/6.3 years of follow up/ ≥128.3 mg/d vitamin C supplementation (1.22, 0.93-1.61, 95% CI) versus ≤52.5 mg/d (R: 1.00, 95%) decreased the risk/alcohol and smoking adjusted (Schuurman et al. 2002).
- 132.837 women and men, 267 liver cancer, 40-71 years of age/9 years of follow up/>109.963 mg/d vitamin C intake (0.71, 0.48-1.04, 95% CI) versus ≤59.928 mg/d (R:1.00, 95% CI) did not make any change/alcohol and smoking adjusted) (Zhang et al. 2012)
- 1806 men, 92 prostate cancers, 21-96 years of age/6 years of follow up/1.47 mg/dL plasma vitamin C concentration (0.77, 0.44-1.98, 95% CI) versus 0.83 mg/dL plasma vitamin C concentration (R:1.00, 95% CI) decreased the risk/alcohol adjusted, smoking not (Berndt et al. 2005)
- 1899 men, 132 men with prostate cancer, 40-55 years of age/30 years of follow up/≥121 mg/d (1.02, 0.85-1.21, 95% CI) versus 74 mg/d (1.07, 0.88-1.29, 95% CI) decreased the risk/alcohol and smoking adjusted (Daviglus et al. 1996).
- 1496 women with breast cancer with postmenopausal period, 866 women with breast cancer in premenopausal women, 2462 controls, 20-76 years of age/10 years of follow up/10 years and longer supplementation of women with breast cancer in premenopausal period with 240 mg/d vitamin C (1.00, 0.75-1.35, 95% CI)-3220 mg/d vitamin C (0.87, 0.64-1.20, 95% CI) and 10 years or longer supplementation of women with breast cancer in postmenopausal period with 440 mg/d vitamin C(1.13, 0.91-1.40, 95% CI) and 3850 mg/d vitamin C (1.24, 0.98-1.56, 95% CI) decreased the risk/smoking and alcohol adjusted (Pan et al. 2011).
- 58.279 men, 939 men with lung cancer, 55-69 years of age/6.3 years of follow up/138 mg/d intake of vitamin C (0.63, 0.49-0.83,

95% CI) versus 51 mg/d intake of the vitamin (R:1.00, 95% CI) decreased the risk/smoking adjusted, alcohol not (Voorrips et al. 2000).

- 34387 postmenopausal women, 879 breast cancer, 55-69 years of age/6 years of follow up/≥392 mg/d vitamin C supplementation (0.88, 0.71-1.09, 95% CI) versus <112 mg/d vitamin C supplementation (R:1.00, 95% CI) had no effect/ alcohol and smoking adjusted (Kushi et al. 1996)
- 58.279 men, 62.573 women, 566 pancreatic cancers, 55-69 years of age/ 130.1 mg/d vitamin C in men (0.92, 0.70-1.21, 95% CI) and 140.5 mg/d vitamin C intake in women (1.00, 0.74-1.33) versus 52. 1 mg/d vitamin C in men (R:1.00, 95% CI) and 58.9 mg/d vitamin C intake in women (R: 1.00, 95% CI) had no effect/alcohol and smoking adjusted (Heinen et al. 2012).
- 1806 men, 62 men with prostate cancer, 21-96 years of age/6 years of follow up/1.47 mg/dL plasma vitamin C concentration (1.42, 0.67-3.01, 95% CI) versus 1.31 mg/dL plasma vitamin C concentration (R:1.00, 95% CI), did not make any change on risk/alcohol and smoking adjusted (Berndt et al. 2005).
- 1548 women, 808 breast cancers, 54.4-56.4 years of age/3 years of follow up/>343.1 mg/d (0.68, 0.47-0.97, 95% CI) versus 142.9 mg/d (R:1.00, 95% CI) decreased the risk/alcohol and smoking not adjusted (Bohlke et al. 1999).
- 12453 women, 37-79 years of age/≥1000 mg/d vitamin C supplementation versus non users who had various cancers (1.33, 1.00-1.76, 95% CI), non users who had breast cancer (1.70, 1.14-2.55, 95% CI), non users who had a family history of cancer (1.16, 0.95-1.41, 95% CI) decreased the risk/alcohol and smoking adjusted (Hutchinson et al. 2010).
- 3123 men and women, 282 gastric carcinoma, 55-69 years of age/ 6.3 years of follow up/96.59±43.85 mg/d vitamin C intake(1.6, 1.0-2.5, 95% CI) versus 103.42±43.03 mg/d (R:1.00, 95% CI) decreased the risk/smoking and alcohol adjusted (Botterweck, van den Brandt and Goldbohm 2000).
- 498 men, 62 men with prostate cancer, 60.2-62.6 years of age/ 6 years of follow up/1.47 mg/dL plasma vitamin C concentration

(1.31, 0.63-2.70, 95% CI) versus 1.31 mg/dL (R:1.00, 95% CI) did not make any effect/smoking adjusted, but alcohol not (Berndt et al. 2005).

- 711891 men and women, 4404 deaths from colorectal cancer, 30-(≥80) years of age/14 years of follow/highest quartile of vitamin C % supplementation (0.89, 0.73-1.09, 95% CI) for ≥10 years decreased the risk/smoking adjusted alcohol not (Jacobs et al. 2001).
- 991522 men and women, 1289 bladder cancer, <40-80< years of age/10 years of follow up/vitamin C supplementation use (≥15 times per month) (0.91, 0.68-1.20, 95% CI) versus non users (R: 1.00, 95% CI) did not make any effect/smoking and alcohol adjusted (Jacobs et al. 2002).
- 299 women, 272 women with breast cancer, 20-69 years of age/ 1 year of follow up/ ≥210.73 mg/d vitamin C intake (0.37, 0.19-0.84, 95% CI) versus <100.20 mg/d (R:1.00, 95% CI) decreased the risk/alcohol and smoking adjusted (Do et al. 2003).
- 4877 women with breast cancer, 444 deaths, 20-75 years of age/4.1 years of follow up/Using vitamin C supplement (0,78, 0.63-0.95, 95% CI) versus no vitamin C supplementation (R:1.00, 95% CI) reduced the mortality risk of breast cancer/ alcohol and smoking adjusted (Nechuta et al. 2011).
- 3346 men, women, 619 bladder cancer, 55-69 years of age/6.3 years of follow up/135 mg/d dietary vitamin C intake (0.74, 0.58-0.95, 95% CI) versus 54.9 mg/d (R:1.00, 95% CI) was not associated with the risk/alcohol and smoking adjusted (Zeegers et al. 2001).
- 62629 men and women, 40-69 years of age/1990-1994/past use of vitamin C supplement (1.17, 1.02-1.33, 95% CI) versus non users (R:1.00, 95% CI) and recent use of vitamin C supplement (1.24, 1.01-1.52, 95% CI) increased the risk of total cancer in women, but did not make any effect in men/alcohol and smoking adjusted (Hara et al. 2011).
- 2974 men, 290 various cancers, 49-59.7 years of age/17 years of follow up/53.1±0.4 μmol/L plasma vitamin C concentration.

- 942993 men and women, 596 control, 82345 skin cancer, 30-79 years of age/16 years of follow up/regular vitamin C users (0.83, 0.68-1.01, 95% CI) versus non users (R:1.00, 95% CI) reduced the risk (Jacobs et al. 2000)/smoking adjusted, alcohol not.
- (1.54, 2.08-2.82, 95% CI) versus 48.7±2.0 μmol/L (R:1.00, 95% CI) did not make any change except stomach cancer/smoking adjusted but alcohol not (Eichholzer et al 1996).

Urokinase plasminogen activator is a serine protease which exists in urine, blood stream and the extracellular matrix. It activates plasminogen and converts it into active form, serin protease (plasmin). Activation of plasminogen by urokinase plasminogen and its conversion into plasmin triggers fibrin production which is the initial response of body to stop bleeding and starts healing of the wounded tissue. But, elevated expression of urokinase (serin protease, plasmin) is correlated with tumor malignancy since the tissue degradation followed by the activation of urokinase plasminogen facilitates tissue invasion and thus contributes to metastasis. The metastatis due to higher levels of urokinase activity makes it a target for many anticancer drugs. Vitamin D_3 and its analogue calcipotriol (MC 903) were reported to decrease its activity of urokinase plasminogen and thus show an antimetastatic effect (Koli and Keski-Oja, 1993; Koli and Keski-Oja, 2000). On the other hand, myofibroblasts that produce and modify the extracellular matrix, secrete angiogenic and pro-inflammatory factors, stimulate epithelial cell proliferation and invasion. These cells are vitally important in wound healing but the inappropriate induction of them leads to organ fibrosis, greatly enhancing the risk of cancer development. A major source of tumor associated myofibroblasts is through transdifferentiation from non-malignant epithelial carcinoma cells through epithelial-mesencyhymal transition. Increased levels of cellular reactive oxygen species stimulate the transdifferentiation to tumor related myofibroblast-like cells, stimulating tumorigenesis (Radisky, Keny and Bissell, 2007). 25-hydroxyvitamin D (25-OHD) increases the expression of antifibrotic factors namely plasminogen activator Inhibitor I and II which inhibit the production of plasmin, plasminogen and myofibroblasts (Artaza and Norris, 2009; Lopes et al. 2012). The inhibition of the mentioned fibrotic factors and increased expression of antifibrotic factors by the vitamin may explain another anticarcinogenic effect of the vitamin.

CYP3A4 (Cytochrome P4503A4), a member of the cytochrome P450 and one of the most important enzymes involved in the metabolism

of various chemicals, antibiotics, pollutants and carcinogens, can be increased via to vitamin D receptors by 1.25(OH)(2)-D(3) (Schmiedlin-Ren et al. 2001; Fukumori et al. 2007).The association between the polymorphisms of cytochrome (CYP) (including the polymorphisms of CYP1A1, CYP1A2, CYP1B1, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP2D6, CYP2E1, CYP3A4, CYP3A5, CYP3A7, CYP8A1 and CYP21 genes) and lung, head and neck and liver cancers is one of the contributers to cancer formation. Besides, there is another important association of CYP polymorphisms with leukemia and lymphomas (Agundez, 2004). Additionally, the activity of CYP is crucially important for the vitamin and its anticarcinogenic effect since the chief circulating metabolite of the vitamin, 25-hydroxyvitamin D is converted into the active hormone 1.25-dihydroxyvitamin D(1,25D) by the cytochrome P450 enzyme CYP27B1 in kidney and other tissues (Jacobs et al. 2013). On the other hand, the vitamin's other anticarcinogenic effect as in association with CYP metabolism may be due to its protection the genes CYP from the polymorphisms by inducing them. Confirming this, CYP3A4 is induced in human intestinal Caco-2 cell model by treatment with1 alpha, 25-dihydroxy vitamin D3 (1,25-D_3) and CYP3A4 in Caco-2 cells is induced by 19-nor-1 alpha, 25-dihydroxy vitamin D_2 in addition to increases in CYP3A4 protein and CYP3A4 mRNA expression both of which are 1-10 nM, 1,25-D3 dose depended (Thummel et al. 2001). The induction of genes, CYPs, by the vitamin and as a result, the detoxification of carcinogens by CYP appears one of the effect mechanism in the antiproliferative effect of the vitamin. Opposite to the anticarcinogenic effect of the induction of CYP by the vitamin, the over expression of CYP, namely CYP24A1, which encodes 24-hydroxylase, the enzyme that converts 1.25(OH)2D_3 to less active calcitroic acid, causes to the increase in the less active form of the vitamin and thus a decrease in antiproliferative effect of the vitamin. The decrease as a result of the CYP24A1 overexpression that leads to the increase in the amount of the less active form of the vitamin and hence the decrease in the antiproliferative effects also indicates to the anticarcinogenic effect of the vitamin (Luo et al. 2013; Segersten et al. 2005).

The suppression of both insulin-like growth factor-1 (IGF-1) and

insulin (which increases the bioactivity of IGF-I) by the vitamin may also decrease the risk of cancer since insulin and IGF-1, not only stimulate anabolic processes as a function of available energy and elementary substrates (e. g. amino acids), but also their signals can promote tumour development by inhibiting apoptosis while stimulating cell proliferation (Kaaks, 2004; Elis et al. 2011; Bartke, 2005; Chitnis et al. 2008; Sandhu et al. 2002). It clearly appears that either a vitamin or its anticartcinogenic effect can not be considered alone in determining its anticarcinogenic potential or its carcinogenic potential due to only the fructose rich content of its food source. The type of the nutrition style and the food composition in the nutrition style act crucially important since high protein and calorie foods like seafood, dairy, meat and refined carbohydrate cause rapid increases in insulin levels and thus leading to increases in IGF-1 signaling while low protein and calorie diet decrease both insulin and IGF-1 levels that may result in cancer prevention (Fontana et al. 2006). One of the important questions which should be highlighted appears at this point that 'how can the fruits and vegetables which are low protein and low calorie and which help to cancer prevention by decreasing the cancer promoters, insulin and IGF-1, be evaluated or included in the list of cancer promoters only due to their high fructose contents!!??. Can it be a completely scientific approach to distort people from consuming fruits and vegetables by only considering their high fructose contents, disregarding their inhibitory effects on cancer promoters, insulin and IGF-1 !!??.Free radicals as one of the radical causes of cancer (Hussain et al. 2003) are molecules or molecular fragments which have one or more unpaired electrons. The presence of unpaired electrons leads into a considerable degree of reactivity upon a free radical. The oxygen derived ones are the most important class in living systems (Valko et al. 2004). Free radical formation and the role of selenium and other antioxidants are based on some important specific biochemical reactions. These are; 1. The superoxide anion radical, formed by the reduction of molecular oxygen mediated by NAD(P)H oxidases, xanthine oxidase or non enzimatically, 2. Superoxide radical which is dismutated by the superoxide dismutase to hydrogen peroxide, 3. Hydrogen peroxide which is the most efficiently scavenged by the enzyme glutathione peroxidase which requires glutathione (GSH) as the

electron donor, 4. The oxidized glutathione (GSSG) which is reduced back to glutathione by the enzyme glutathione reductase which uses NADPH as the electron donor, 5. Some transition metals (e. g. Fe^{2}+, Cu+ and others) can break down hydrogen peroxide to the reactive hydroxyl radical (Fenton reaction). Because the DNA backbone is composed of negatively charged phosphate groups, metal ions such as Na+, Mg^{2}+, Fe^{2}+, Fe^{3}+, Cu+, Cu^{2}+, etc. are localized via electrostatic interaction near the phosphate backbone of DNA. When H_2O_2 is present as a result of heavy oxidative stress and antioxidant poor nutrition, redox active metal ions such as Fe^{2}+ or Cu+ that are bound to the DNA react with H_2O_2 to form highly reactive 'OH' radical (Peron and Brumaghim 2009). OH may damage the nucleotide bases in DNA resulting in oxidized base products such as 8-oxo-guanine (Lu et al. 2001) which causes further damages on DNA of healthy cells thus increase the risk of cancer. When the damage caused by the reactive hydroxyl radical on DNA (which may often appear as an important contributor to cancer formation) is considered, antioxidants; ascorbic acid, alpha-tocopherol and 25(OH) D were claimed to inhibit OH-induced deoxyribose degradation while scavenging superoxide anion and nitric oxide radicals (Singh et al. 2009; Nail-Shalliker et al. 2012), 6. OH radical not only damages DNA, but also may start oxidation by abstracting an electron from polyunsaturated fatty acid, yielding a carbon-centered lipid radical which can further interact with molecular oxygen to give a lipid peroxy radical. If the lipid peroxy radical is not reduced by antioxidants namely vitamins, D and E, carcinogens may form from the further peroxidation of lipid peroxy radicals. Especially, vitamin E shows a specific and extraordinarily important antioxidant effect at this point that the lipid peroxy radical is reduced within the cell membrane by the reduced form of vitamin E, forming a lipid hydroperoxide and a radical of vitamin E. The radical formation from vitamin E which has got neither carcinogenic nor oxidative effect when compared with the production of oxidative and carcinogenic lipid peroxy radicals may naturally decrease the amount of carcinogenic free lipid peroxy radicals. Besides vitamin E, another antioxidant, vitamin C shows a similar antioxidant and anticarcinogenic effect by regenerating vitamin E. Vitamin C reduces the radical of vitamin E back to anticarcinogen and antioxidant vitamin E, leaving

behind the ascorbyl radical that has neither carcinogenic nor oxidative, which was rather shown with its anticarcinogenic, antiproliferative and proapototic effect on human pancreatic cancer cells (PANC1) (Mukai et al. 1991; Nagaoka et al. 2007; Hamre et al. 1997; Halpner et al. 1998; Naidu et al. 2003). Thus, not only the importance of vitamin C and E alone, but also their synergism in cancer prevention via to minimizing lipid peroxy radicals appears as vitally important in cancer prevention. The damage of DNA by OH and heavy toxic metals and the damage on cell membranes by free peroxy radicals increase the ratio of cytochrome c and TUNEL-positive cells. Cytosolic cytochrome c is a kind of small heme protein which are normally found as associated with the inner membrane of the mitochondrion, but it passes into cytoplasma from the membrane under oxidative damage and hence, its concentration increases with the increase of oxidative stress and free radicals. Another indicator of heavy oxidation and inflammation besides cytosolic cytochrome c is the TUNEL-positive cells, the cells with their damaged and fragmented DNA, detected by a method called TUNEL. Vitamin D_3 has been claimed to decrease the increased cytosolic cytochrome c and TUNEL-positive cells during DNA damage in iron-induced neurotoxicity (Chen et al. 2003). Therefore, one of the antioxidants and anticarcinogens, glutathione (GSSG) that contains selenium in its structure, the antiproliferative and proapoptotic ascorbyl radical which is formed as a result of vitamin E regeneration by vitamin C, the convertion of oxidized glutathione back to glutathione in anticarcinogenic effect by Omega 3 fatty acids, dihydrolipoic acid (DHLA) and α-lipoic acid (ALA) and the direct anticarcinogenic effect of vitamin D_3 during DNA damage by decreasing the amounts of TUNEL positive cells and cytochrome c, bring up the importance and necessity of the combined consumption of foods rich in selenium, Omega 3 fatty acids (DHLA and ALA), vitamins C, E and D_3 rather than their sole consumptions. Despite the unlimited number of antioxidant formulas containing various antioxidants in their formula and the widespread public information about them, there seems neither a study as related to the combined use and effect of selenium, α-lipoic acid (ALA), vitamin C, dihydrolipoic acid (DHLA), vitamin E and vitamin D_3 nor any public education about the necessity of their combined use in cancer prevention.

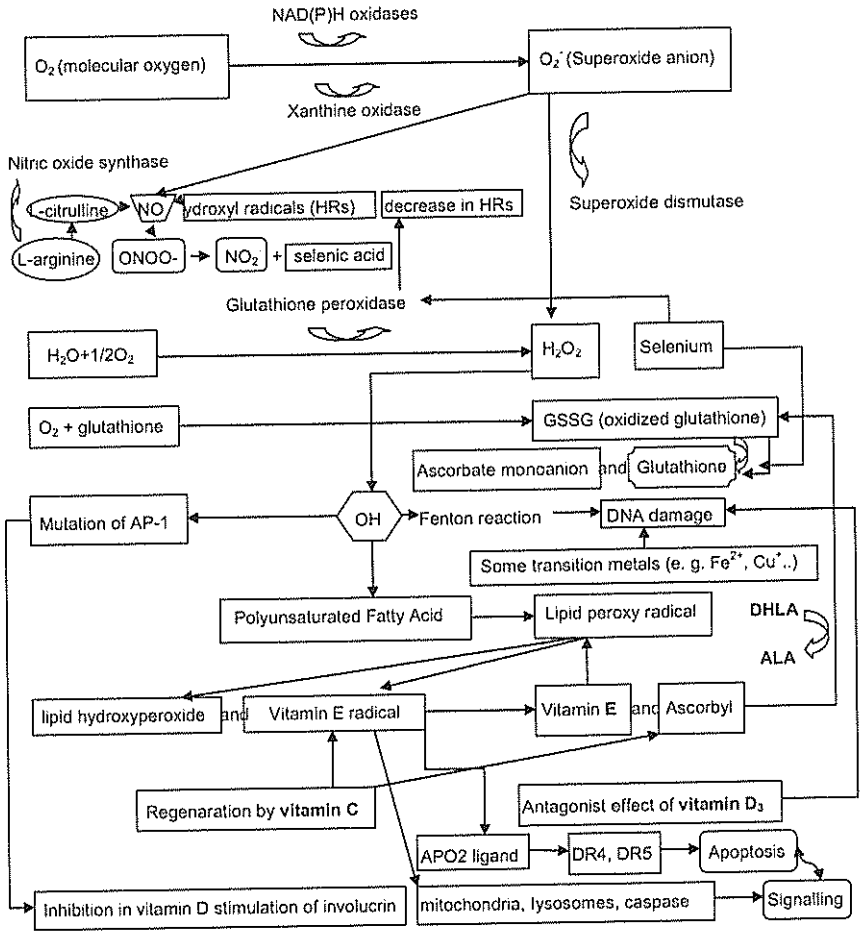


FIGURE 19

The increased activity of endothelial lipase in cancer cells is one of the great contributers to tumor invasion since the increased activity of them regulates oxidation, the process to yield energy and free radicals by combusting fats with oxygen. The increased energy helps for the proliferation of cancer cells while the free radicals damage healthy cells. Similarly, gastric cancer, as one of the most common malignant tumors in the world, has been reported to a higher level of endothelial, monoacylglycerol and triglyceride lipase activity (Dong et al. 2013, Nomura et al. 2010; Das and Hoefler, 2013). However, the

vitamin (calcitriol) was determined to decrease the lipoprotein lipase concentration in 3T3-L1 adipocytes (Querfeld et al. 1999). When the important contribution of the mentioned endothelial, monoacylglycerol and lipoprotein lipases to cancer is considered, the inhibitory effect of the vitamin on these lipases may form another anticarcinogenic potential of the vitamin.

Involucrin, the major protein of the cornified envelope of keratinocytes, provides much of the structural integrity of skin. Mutation of the AP-1, the activator protein which regulates gene expression in response to a stimuli like infection, stress, cytokines and growth factor and controls the cellular processes; differentiation, proliferation and apoptosis (Ameyar et al. 2003) is shown to reduce and block 1.25-dihydroxyvitamin D_3 stimulation of the involucrin (Bikle et al. 2002). On the other hand, the expression of involucrin was shown to decrease by 80.8 % in three severity levels of cervical intraepithelial neoplasia (CIN 1, 2, 3) (Xu et al. 1999) while increasing healing of wounds in epidermis (Li et al. 2000). Thus, the deficiency of the vitamin may lead to the insufficient stimulation of the protein by the vitamin. As a result, the decrease in involucrin due to the vitamin deficiency which may ease the invasion of tumour cells may be another anticarcinogenic effect of the vitamin.

NF-kβ, (Nuclear factor kappa light chain enhancer of activated β cells), a protein complex that controls the DNA transcription, is found in almost all animal cell types and involved in cellular responses to stimuli such as stress, free radicals, cytokines, ultraviolet irradiation, low density lipoprotein (bad cholesterol), bacterial and viral antigens. Aberrant regulation of NF-kβ and the signalling pathways between NF-kβ and the mentioned stimuli are involved in cancer development and progression including the resistance to chemotherapy and radiotherapy (Baud and Karin 2009; Karin et al. 2002). Confirming this, breast carcinoma cell lines; HCC 1937, HCC1954, HCC70, HCC38, HCC1143, MB231, BT549, MB436, T47D, MCF7 and MB453, were shown to have increased by the activation of NF-kβ (Yamamoto et al. 2013), showing a strong correlation between this activation and the proliferation rates in the cancer cell lines. On the other hand, NF-kβ activity and cancerous cell proliferation rate via to NF-kβ can be reduced by 1.25-dihydroxyvitamin

D_3 (Cohen-Lahav et al. 2006; Tse et al. 2010 and Krishnan et al. 2010) that this reduction may be another contributer to the anticarcinogenic potential of the vitamin.

Another anticarcinogenic effect of the vitamin stems from its effect on the small 165 amino acid protein p21 which mediates the tumour suppressor protein p53, the gene that is involved in the control of cell growth with an antiproliferative effect on tumor cells by binding to GADD45 (Growth Arrest and DNA Damage Inducible genes) (Zhan et al. 1994). Vitamin D analogues; calcitriol, 1.25-dihydroxy-16-ene-23-yne vitamin D_3 (16,23-D3) or 22-oxa-1.25-dihydroxyvitamin D_3, were claimed to attenuate retinoblastoma and pancreatic tumor growth in athymic mice pancreatic cancer cell lines and MG-63 osteocarcinoma cells by increasing apoptosis and upregulating both p53, p21 and p27 which are the potent tumour suppressor proteins (Audo et al. 2003; Kawa et al. 1997; Zenmyo et al. 2001). In addition to the close relation between the tumor suppressor p53 and GADD45, the genes GADD45 also regulate the NF-kappaβ activity and an inhibition of NF-kappaβ in cancer cells results in GADD45 alpha and gamma dependent induction of apoptosis (Zerbini and Libermann, 2005). Confirming this, the gene GADD45Y expressed by 1.25-(OH)2D3, has been shown to inhibit malignant prostate epithelial cells through the inhibition on the progression of G1 to S phase cell cycles (cycles that comprise the long growth period of the cell cycle before cell division and mitosis) (Flores and Burnstein, 2010).

Another indicator for the anticarcinogenic potential of the vitamin is the vitamin receptors. These receptors linked in the synthesis and degradation of vitamin D have been identified in many non-neoplastic peripheral tissues including colon, pancreas, brain, lymph nodes, suggesting a role for the vitamin in the regulation of normal cellular growth (Lehmann et al. 1998; Holick et al. 2003). Confirming this, vitamin D works as in cooperation with the retinoid-X receptor and also another receptor, the retinoid A. The vitamin D receptor as in combination with these two receptors binds to the vitamin D response element in the target genes (Kliewer et al; Beer and Myrthue, 2004). The genes that involve the vitamin D response elements are; bone related genes (osteocalcin, osteopontin), the calcium binding proteins

calbindin-D28k and D9K fructose 1.6 bisphosphatase, parathyroid hormone, parathyroid hormone-related protein (Christakos et al. 2003; Osborne and Hutchinson, 2002). This binding interacts with coactivator complexes which link to the RNA polymerase complex and initiates transcription. Thus, there is a close link between the vitamin and normal and abnormal cell growth. As a result, any deficiency of the vitamin may result in cancer causing cell proliferation via to the effect of the vitamin on these receptors. The mentioned relation between parathyroid hormone genes that involve the vitamin D response elements explains one of the anticarcinogenic effects of the vitamin. The vitamin, the ultraviolet which promotes dermal vitamin D generation and the dietary calcium which suppresses parathyroid hormone (the hormone which increases the hepatic production of the progression growth factor IGF-1) are the contributers of the anticancerogenic effect of the vitamin. Besides, parathyroid receptors mediate co-mitogenic and/or pro-invasive signals in some cancers (McCarty 2000) that the suppression of parathyroid hormone receptors by the vitamin, the vitamin and ultraviolet or calcium, interrupt these signals which may result in cancer prevention (McCarty, 2000). Confirming this, increased expression of the parathyroid receptor and parathyroid hormone promote the growth and invasiveness of prostate cancer cells in bone (Schwartz, 2008).

TNF ligand and cognate TNF receptor superfamilies are involved in diverse biological processes ranging from the selective induction of cell death in potentially dangerous to providing signals that help for an effective immune response (Bremer 2013). The diverse biological processes are directed by TNF including apoptosis, inflammation and immunity. Its current use in cancer is the treatment of locally advanced soft tissue sarcomas and metastatic melanomas. Its action in cancer begins with extravasation of erythtocytes and lymphocytes which results in hemorrhagic necrosis. It targets the tumor-associated vasculature by inducing hyperpermeability and destruction of the vascular lining. Induction of hyperpermeability and distruction of the vascular lining by TNF alpha cause the selective accumulation of cytostatic drugs inside the tumor. Thus, it is commonly being used as combined with cytostatic drugs in cancer cells due to its mentioned synergism with these drugs (van Horssen et al. 2006). In spite of its important synergism

with cytostatic drugs in cancer, TNFα has also systemic toxicity which limits its use in cancer treatments. It has been implicated in both cancer development and progression (Mocellin and Nitti, 2008). However, cell based therapy, pre-targeting, TNFα fusion proteins are already in advanced clinical trials to reduce the toxicity of TNFα on healthy cells (Cai et al. 2008). TNFα is the most debated cytokine because of the studies which claim its carcinogenic effect rather than anticarcinogenic (Ferrajoli et al. 2002; Liu et al. 2000). Conflicting with all these adverse toxicity risks of the gene, the triggering effect of vitamin D on TNFα was found as inhibitory on some cancer cells in some of the studies. 1 alpha, 25-dihdroxyvitamin D_3 (calcitriol) and its analogue CB1093, were reported to have up-regulated TNF-alpha mRNA expression in human prostate cancer cell lines; LNCaP and PC-3. Both calcitriol and CB1093 were determined to enhance the production of TNF-alpha (Tumor Necrosis Factor-alpha) in LNCaP cells. As a result of TNF-alpha production by the vitamin and CB1093, the vitamin could induce apoptosis in prostate cancer cells and thus the vitamin and its analogue may play an important role in the control and treatment of prostate cancer (Golovko et al. 2005). Similarly, the anticarcinogenic effect of the vitamin, calcitriol on breast cancer cells due to its inducing effect on TNFα was also claimed in some other studies (Weitsman et al. 2003; Lopes et al. 2012). Because of these conflicted study findings related to the effect of TNFα on cancer, its relation with vitamin D, is also debated. The widest review about TNF α which belongs to Mocellin et al. (2005), explains the conflicting results of the studies about the effect of TNFα on cancer by taking two different timing and dose related applications of TNFα. According to the review, a high-dose single-shot TNFα based regimens can induce tumor-regression in in-vivo animal and human models however an endogenous low-dose TNFα chronically produced within the tumor microenvironment is associated with cancer development/progression in some preclinical models. Considering the important deductions of the review and the relation between vitamin D and TNFα, a high dose single shot TNFα based regimen plus vitamin D therapy may be promising which strongly needs further studies to highlight its effect in cancer treatment.

The peptide and antibody inhibitors of fibronectin (the extracellular

matricx compound) and integrin (surface adhesion molecules) have been shown to be the effective inhibitors of metastasis (Akiyama, Olden and Yamada, 1995). 1.25 (OH)(2) vitamin D_3 was shown to induce the accumulation of alpha (v)-integrin, beta(5)-integrin, both of which have tumor suppressors, important signaling pathways to apoptosis (Stupack and Cheresh, 2002). Thus, the vitamin is suggested to revert the myoepithelial features associated with more aggressive forms and poor prognosis in human breast cancer (Pendas-Franco et al. 2007). The vitamin has been defined as a key in the attenuated expression of fibronectin (Polly et al. 1996) and it may inhibit tumor invasion due to its enhancing effect on fibronectin. The thyroid cancer cells and the melanoma associated antigen (MAGE A3) gene both show an up-regulated response to fibronectin silencing, stimulating the growth of cancer cells Liu et al. 2008). Both 1.25-vitamin D_3 and EB1089 increased cell adhesiveness with a consistent increase in fibronectin expression. Confirming this, attenuated fibronectin expression was associated with a relative intensitivity to 1.25 vitamin D3 growth-suppression action ((Liu, Asa and Ezzat 2005). These findings may indicate to the anticarcinogenic potential of the vitamin due to its mentioned inhibitory effect on cancer cells by stimulating the upregulation of fibronectin and intergrin expression.

Like vitamin E, vitamin D (1,25(OH)(2)D(3)) increases the expression of VEGF which induces the progress of cancer by angiogenesis. This increase forms by the binding of vitamin D receptor of two response elements in the VEGF promoter which is activated followed by this binding (Cardus et al. 2009; Zhong et al. 2014; Jamali et al. 2014). Therefore, the regular vitamin D rich food consumption which includes the great amounts of liver oil, swordfish, salmon, tuna fish, milk, yogurt, sardines, liver, egg, orange juice (fortified) and cheese and/ or vitamin D supplements (USDA 2014), should be avoided during the treatments with the VEGF inhibitors; sunitinib, sorafenib, bortezomib, bortezomib and MP 0250 combination, MG132, MG262, KF58333, 17-AAG, geldanamycin, SNX-2112, honokiol, thapsigargin, bafilmycin A1, budesonide, brefeldin A, monensin, ritonavir, bevacizumab, ranibizumab, fulvestrant and vandetanib combination, tamoxifen, clomiphene, nafoxidine [ICI182,780], metformin, paclitaxel, tunicamycin

and PTK787/ZK222584 (vatalanib) since the mentioned anti-cancer agents target tumors by inhibiting VEGF, opposite to the vitamin.

The vitamin (calcitriol), the hormonal form of vitamin D, enhances TNF-induced cytotoxicity in breast cancer cells and induces caspase-3-like activity and ROS-mediated caspase-dependent cell death (Weitsman et al. 2003). So, the anti-cancer agents which target cancer cells by activating caspases and subsequently inducing ROS influx; sorafenib, tetrandine, cisplatin, bortezomid, vorinostat, MG-132, metformin, thapsigargin, tunicamycin, 17AAG, DBeQ, ritonavir and brefeldin A and sunitinib, may benefit from the use of vitamin D or calcitriol supplementation or vitamin D rich nutrition since both the vitamin and the anti-cancer drugs induce ROS influx via the activation of caspases.

Vitamin D may inhibit the cancer cells by suppressing COX-2, the inflammatory and cancerogen hormone (Wang et al. 2014; Aparna et al. 2008). The inhibition of COX-2 by the vitamin may be one of the anti-cancer effects of it while this attribute may enhance the anti-cancer and anti-inflammatory effects of the anti-cancer drugs which similarly inhibit COX-2, the anti-cancer drugs namely; sunitinib, celecoxib, magnolol, honokiol, eugenol, bis-eugenol, tetrandrine, 17AAG, raloxifene, rofecoxib, nafroxen, dexamethasone, hydrocortisone, triamcinolone acetonide, methyl prednisolone and beclomethasone diproprionate, creating a synergy among the vitamin and the anti-cancer drugs via the inhibition of the inflammatory protein.

The metabolite of vitamin D, 1 alpha, 25-dihydroxy vitamin D(31,25(OH)2D3) inhibits beta-catein transcriptional activity by promoting vitamin D receptor (VDR) binding to beta-catenin and the induction of E-cadherin (a transmembrane protein like beta-catenin, but it plays important role in cell to cell adhesion) expression. Recently, 1,25(OH)2D3 has also been shown to distinctly regulate the two genes encoding the extracellular Wnt (the proteins which produce Wnt signaling and pass this signal into the cell through cell surface receptors) inhibitors; DICKKOPF-1 and DICKKOPF-4 (DKK-1, DKK-4) (Pendas-Franco et al. 2008). Confirming this data, Hes-1, a downstream factor of the Notch signaling pathway enhances 1.25(OH)(2)D(3)-induced transcription of osteopontin (OPN), a glycosylated phosphoprotein that binds calcium in bone extracellular matrix while the targeted distruption of the vitamin D

receptor (VDR) or Runx2 (Runt-related transcription factor 2), a protein and transcription factor for the osteoblast differentiation, results in a marked inhibition of the osteopontin (OPN) expression in osteoblasts (Shen and Christakos 2005). Wnt/beta-catenin pathway, the signal transduction made by proteins that pass signals from outside of a cell to the inside which results in the accumulation of beta catenin and the formation of malignancies, may be inhibited by the vitamin's mentioned inhibitory effect on beta-catenin by binding VDR to beta-catenin and its regulatory effect on the extracellular Wnt inhibitors. Therefore, the combined use of vitamin D or calcitriol supplements or vitamin D rich foods with the B-catenin inhibitors; sunitinib, sorafenib, SCH727965, metformin and bortezomib combination, tunicamycin, radicicol, KUSs, versipelostatin, pyrivinium pamoate, tanespimycin and 17-AAG, may enhance the anti-cancer effects of these inhibitors, creating a synergy via the inhibition on B-catenin.

Erbb2 (Receptor tyrolsine-proteine kinase, also known human epidermial growth factor receptor 2, HER2), a glycoprotein which is a proto-oncogene and a member of the human epidermal growth factor receptor family whose overexpression leads to the progression of breast cancer, is inhibited by the vitamin D analog BXL0124 (So et al. 2013). Therefore, quercetin rich foods; lettuce, green pepper, asparagus, red leaf, tomato, Romaine lettuce, apple, red grape, broccoli, onion, caper, cranberries, cherries, green tea, black tea, cocoa and orange juice, cheese, sardines, yogurt, liver oil, quercetin and/or vitamin D (or calcitriol) supplements may be beneficial during the anti-cancer treatments which administer Erbb2 (HER2) inhibitors; lapatinib, afatinib, neratinib, canertinib, sapitinib, AC480, TAK-285, CUDC-101, AEE788, tryphostin AG879, tyrphostin AG825, mubritinib, SKLB1206, sorafenib, trastuzumab and saracatinib, sine all all the mentioned bio-active compounds and the drugs may form a synergy via the inhibition of Erbb2 (HER2).

The vitamin in the form of calcitriol and cholecalciferol (steroid molecule form of the vitamin with one ring open), may show one of its anti-cancer effect by repressing the Hedgehog(Hh) signaling, the signaling which transfer information to embryonic cells for the cell development and survival (Albert and Hahn 2014; Tang et al. 2011;

Cortes et al. 2015; Uhmann et al. 2012). The mentioned inhibitory effect of the vitamin on the signaling, may enhance the anti-cancer potential of Hh inhibitors; SANT1-SANT4, CUR-61414, HhAntag-691, GDC-0449, saridegib, phthaladines, mukul, guggulsterone, itraconazole, NVP-LDE225, TAK-441, XL-139, HTS piperidines, MRT-92, MRT-83, PF-04449913, N-acylethanolamides, endocannabionids, IPI926, BMS-833923, LEQ506, GANT61, ribotnikinin, HPI1-4, 2-acylglycerols and 2-alkylglycerol, if these inhibitors are administered as combined with D3 or/and calcitriol supplements or/and vitamin D rich foods.

One of the most crucial points to concern in anti-cancer nutrition is the association between vitamin D and Notch (DSL) proteins, the proteins whose interaction with their cell-bound ligands build up an intercellular signaling pathway, a central pathway and key in the development of angiogenesis. The deficiency of the vitamin down-regulates the Notch pathway (Domingues_Faria et al. 2014). The resistance of the glioblastoma multiforme cells against the antiproliferative effects of 1.25(OH)2D3, detected by Reichrath et al. (2010), may support the claim of Domingues-Faria et al. (2014). As in the highlight with the mentioned data of Notch and the vitamin, it can be expressed that the vitamin induces the Notch signaling while the deficiency of it inhibits. Therefore, it may be severly important, crucial and beneficial to avoid calcitriol or/and 1.25(OH)(2)D(3) or/and vitamin D(complex) supplements or/and vitamin D rich foods during the anti-cancer treatments which administer the Notch signaling inhibitors; OMP-59R5 anti-Notch 2/3 mAb, NRR1 anti-Notch1mAb, NRR2 anti-Notch2mAb, DLL1-Fc, JAG1-Fc Anti-Delta-like 1, Jagged 1 Fc chimeric mAbs, A5622A anti-nicastrin mAb, RO4929097, MRK-003, MRK0752, PF-03084014, MAM peptide antagonist and PF-03084014, since the vitamin may be contraindicated with the mentioned inhibitors since it has got opposite effect as mentioned. It may be beneficial to note that opposite to vitamin D or its different forms, the quercetin and quercetin rich foods may be useful during the same anti-cancer treatments, creating a synergy via inhibition of Notch signaling.

Another important item and conflicted status for the vitamin is its effect on p38, the mitogen-activated protein kinase which can inhibit cell growth by decreasing the expression of cyclin D. Nonn et al. (2006)

claims the inhibitory effect of the vitamin p38, while Pardo et al. (2006), Daniel et al. (2004), von Essen et al. (2010) and Qi et al. (2002), have found the opposite, stimulating effect of the vitamin on the gene.

MAP kinases such as JNK or the mentioned p38 are the central signal transducers of inflammatory signals during cancer while the stimulation of the signaling depends on the stimulus, cell type and the response (Miodovnik et al. 2012). In the claims of Pardo et al. (2006), Daniel et al. (2004), von Essen et al. (2010) and Qi et al. (2002), the response is the formation of an inflammation to destroy the causative agent (e.g.virus, bacteria..) via the induction of p38 by 1α, 25(OH)2D3. But when the inflammation is considered, vitamin D inhibits the production of proinflammatory cytokines like IL-6 or TNFα via inhibition of p38 (Zhang et al. 2012). Under the consideration of the inhibitory effect of the vitamin o p38, vitamin D/calcitriol/1α,25(OH)2D3 supplements or vitamin D rich foods may enhance the anti-cancer and anti-inflammatory potentials of the p38 inhibitors; doramapimod, VX-745, VX-702, AMG-548, Scio-323, Scio-469 and pamapimod, creating a synergy via the inhibition of p38.

Vitamin D (1α,25(OH)2D3) enhances binding of FOXO proteins, FOXO3a and FOXO4, the proteins which act as tumor suppressors, to promoters of FOXO target genes while vitamin D(1α,25(OH)2D3) rapidly (in <4h) induces FOXO deacetylation and dephosphorylation, consistent with FOXO activation (An et al. 2010) since deactylation by sirtuin 1 and class III histone deacetylase (HDAC) induce FOXO transcription and this induction results in FOXO activation (Hariharan et al. 2010).

The mentioned activation of tumor suppressor FOXO proteins by the vitamin enhance the anti-cancer potential of the anti-cancer treatments which administer FOXO activators; metformin, doxorubicin, nipradilol, timolol, melatonin, withaferin A, bortezomib, vorinostat, tunicamycin, paclitaxel, geldanamycin, AZD5363, cisplatin and 5-aza-2-deoxycytidine if the supplements of the vitamin or the vitamin rich foods are combined with these activators, via the synergy to induce FOXO activation.

Although Nrf2, the transcription factor encoded by the NFE2L2 gene (Moi et al. 1994), regulates detoxification and antioxidant defenses and inhibit ROS production as a strong antioxidant, cancer cells like the

healthy cells exploit the antioxidant function of the factor and protect themselves against ROS by using this factor. Therefore, as previously mentioned in the related part with Nrf2, Nrf2 inducers; BM31, BM10, BM40, 2-cyano-3, 12-dioxooleana-1, 9-dien-28-oic acid-methyl amide, tBHQ, 3H-1,2-dithiole-3-thione, sulforaphane, tanshinone 1 dihydrotanshino, BHA, ethoxyquin and I3C are contraindicated with the anti-cancer agents which target cancer cells by producing ROS, the anti-cancer agents namely; sunitinib, sorafenib, tetrandine, cisplatin, bortezomid, vorinostat, MG-132, metformin, thapsigargin, tunicamycin, 17AAG, DBeQ, ritonavir and brefeldin A. More important is the contraindication of vitamin D if vitamin D rich foods or supplements are combined with these ROS producing drugs, since the vitamin activates Nrf2 (Nakai et al. 2014; Manna and Jain 2015). Although, there is currently no study which directly highlight the association of the vitamin with ERalpha, it is well known that the vitamin D receptor (VDR) gene activates ERalpha and the vitamin D receptor interacting protein (DRIP150) (Colin et al. 2003; Lee and Safe 2007; Zhang et al. 2003). So, there may always be a risk that, the vitamin rich foods or supplements may trigger ERalpha via activation of VDR and DRIP150. For this reason, it may be a beneficial approach to avoid from vitamin D supplements and vitamin D rich foods during the anti-cancer treatments which use ERalpha inhibitors; nafoxidine, hexestrol, C1618 and dinestrol, especially during berast cancer.

One of the most important items to concern about the vitamin during the anti-cancer treatments is the association of the vitamin with VDR/PI3K/Akt pathway that PI3K and Akt, the anti-apoptotic proteins are cross-activated by VDR, making the pathway as a survival pathway for cancer cells (Zhang and Zanella 2008; Borges et al. 2016; Hughes et al. 2008). This detail seems to have an uppermost importance, particulary during the anti-cancer treatments which administer PI3K/Akt inhibitors; LY29002, SF-1126, NVP-BEZ235, XL147, XL765, ISC-4, GSK690693, MK2206, fused pyrimides, PIP3, GDC-0941, celecoxib, UCN-01, BX-795, BX-912, BX-320, CCT128930, GDC-0068, perifosine, GSK-214795, BX-320, GSK2110183, ipatasertib, afuresertib, AT13148, PF-04691502, A47867 and triciribine, if these anti-cancer drugs are administered as combined with a vitamin D rich nutrition and/or vitamin D supplements,

since the vitamin may be contraindicated with them by activating the anti-apoptotic PI3K/Akt pathway and subsequently cell survival.

Two positive regulators for cell proliferation in cancer are 'cyclins' and 'cyclin dependent kinases' (CDKs) that CDKs are activated by cyclins for the maintanence of cell cycle. Another important signal transduction for cell proliferation is the Ras/Raf pathway. Ras is a proto-oncogene and Raf is a serine/threonine kinase. The Ras/Raf signal transduction activates the CDKs, namely; Raf, Src, MAP (Mitogen Activated protein) and ERK1/2 (Extracellular signal-regulated kinases 1 and 2). This activation results in the expression of genes which are required for cell cycle and cell division (Chakraborti et al. 2011). On the other hand, there are two important negative regulators of the cell cycle and growth; CDK inhibitory protein (CIP) family (e.g.proteins p21, p27 and p57) and the inhibitors of kinases (e.g. proteins; p16, p19 and p15). CDK inhibitors (CDKIs) bind cyclin/cdk complexes and inhibit their proliferation promoting effects. Similarly, p21 inactivates cyclin/cdk complexes and subsequently inhibits cell cycle progression through G1 phase. The damaged DNA by p21 cannot enter into S phase, leading to apoptosis. On the other hand, vitamin D(1α,25(OH)2D3) activates p21, p27, p53 (Zenmyo et al. 2001; Kawa et al. 1997; Audo et al. 2003; Saramaki et al. 2006). The very promosing anti-cancerogenic effect of the vitamin via the activation of CDKIs; p21, p27 and p53, may be enhanced if the vitamin D supplements or vitamin D rich foods are combined with the CDKIs; palbociclib, fulvestrant, tamoxifen, honokiol, MCS-C2, flavopiridol, brefeldin A, ritonavir, thapsigargin, NU6140, 17-AAG, purine olomoucine, purvalanol B, roscovitine, ZK304709, PD-0332991, SNS-032, SCH-727965, AZD5438, AT7519, RGB-286638, SNS-032, SCH-727965, P1446A-O, P-276-00, p21WAF1/Cip1, MI-63, HL198, CDB3, 37AA, JJ78, tenovin-b, MI-21, MI-43, gatifloxacin (whose anti-cancer via the inhibition of p21, p27 and p53 by Akt iinductionHL198, MF-219, CP-31398, p21WAF1/Cip1 and KILLER/DR5 and KILLER/DR5, creating a synergy via the activation of the CDKIs; p21, p27 and p53. Akt (protein kinase B; PKB) which contributes to cell proliferation via phosphorylation of the CDK inhibitors p21, p27 and p53 (Lawlor and Rotwein 2000, Rössig et al. 2001; Astle et al. 2012; Kim et al. 2010).

The vitamin (1α,25(OH)2D3) suppresses the Akt/NF-kB/COX-2

pathway (Wang et al. 2014) which appears as it is one of the anti-cancer effects. This anti-cancer potential of the vitamin via the inhibition of Akt (which is directly reflected as the induction of the apoptotic proteins p21, p27 and p53) may be improved if the Akt inhibitors; LY29002, SF-1126, NVP-BEZ235, XL147, XL765, ISC,4, GSK690693, MK-2206, fusedpyrimides, PIP3, GDC,0941, celecoxib, UCN-01, BX,912, BX-320, CCT128930, GDC-0068, perifosine, AT13148, PF-04691502, A47867 and triciribine are combined with the vitamin D supplementation or the vitamin rich foods since both the inhibitors of Akt and the vitamin may create a synergy via the inhibition of Akt and as a result the induction of the pro-apoptotic proteins; p21, p27 and p53. Finally, one of the crucial concerns about the vitamin, in spite of many of its anticancerogenic effects mentioned above is the risk of the activation of the anti-apoptotic ERK signaling (Narayanan et al. 2004). Therefore, the anticancerogenic treatments that use the following ERK inhibitors; vorinostat, ritonavir, radicicol, tamoxifen, geldanamycin, lapatinib, fulvestrant, PD98059, UO126, honokiol and SNX212, may be contraindicated with the vitamin D supplements or te vitamin rich foods because of the inducing effect of the vitamin on the anti-apoptotic ERK signaling, as opposite to the mentioned ERK inhibitors.

Bcl-2 and Bax (Bcl-2 associated x protein) are in close relation during and prior to cancer that Bax acts as a proapoptotic protein while Bcl-2 under some conditions, acts as anti-apoptotic. But, both the mentioned effects of both Bcl-2 and Bax are regulated and determined by p53. Vitamin D, by the means of a p53 dependent mechanism, upregulates BAX while leads to the downregulation of Bcl-2 (Chakraborti et al. 2011). Because of the mentioned inducing effect of the vitamin on Bax, the Bax inducers; actinomycin D, apicidin, gossypol, AT-101, BAM7, cyclophosphamide, gambogic acid, kaempferol, mitomycin-c, oxaliplatin, 2-methoxyestradiol, 2-indolinones, piperlongumine, plumbagin, streptozotocin, genistein, diallyl sulfide, lycopene, I3C, arginine and sulforaphane, may have stronger apoptotic effect if they arer administered in anti-cancer treatments as combined with the vitamin D supplements or vitamin D rich foods. Accordingly; the inhibitors of the anti-apoptotic proteins, Bcl-2; HA14-1, AT-101, obatoclax, ABT-263, ABT-737, sunitinib, sorafenib, thapsigargin, bortezomib, 17-AAG, vorinostat, honokiol, metformin, tetrandrine, tamoxifen, geldanamycin,

radicicol and raloxifen, may benefit from the vitamin D supplements or the vitamin rich foods due to a possible synergy via the inhibition of the anti-apoptotic Bcl-2 proteins, leading to apoptosis.

Limitations for vitamin D: Inspite of a great number of data that shows the anticarcinogenic potential of the vitamin, a limited amount of studies have conflicted results. But some of these studies which claim the opposite effect of the vitamin have some limitations which decrease the sensitivity of their findings. For example Eide et al. (2011) claims the adverse effect of the vitamin on nonmelanoma skin cancer but the cancer type studied in this cohort directly limits the accuracy of the findings since nonmelanoma cancer is one of the initial cancer types which is significantly affected by ultraviolet. Thus, the findings may not have clearly determines the origin of the effect whether it comes from ultraviolet or the vitamin. Similarly, the sex is another factor which limits such studies claiming the harmful effect of the vitamin on cancer like in the study of Kilkkinen et al. (2008). The authors found a significantly important anticarcinogenic potential of the vitamin on lung cancer in women, but not in men. Another limitation which may lack the sensitivity of study findings about the anticarcinogenic potential of the vitamin is its existence in different amounts in vitamin D or complex supplement tablets. The amount of the vitamin in these supplements ranges from 10 μg (400 IU) to 50 μg (2000 IU) (Lappe et al. 2007) while the tolerable upper intake limit of the vitamin from foods or supplements without any adverse effect for children and adult is informed as 25 μg (1000IU)/d. Similarly, the 'form' is another determiner for the vitamin's anticancerogenic potential as clearly can be understood from the findings of the mentioned cohorts above. Confirming this, calcitriol (1.25-dihydroxycholecalci and Mathiasen et al. 2002; Beer and Myrthue 2004) is the form of the vitamin with a different and special anticarcinogenic effect by stimulating apoptosis and prompting the release of calcium from special storage spots inside cells and blocking the production of proteins that prevent cell death while enhancing the production of proteins that cause cell death.The fact that there is no standart amount of the vitamin and its form in supplements may naturally affect its anticarcinogenic potential, not only in the related scientific studies, but in the metabolism of the individuals in their daily lives or cohorts.

The STUDIES about the ASSOCIATION of VITAMIN D and CANCER

- 171 colorectal cancers, 280 controls, 30-75 years of age/ 5 years of follow up/5.3 μg/d (1.00, 0.5-2.1, 95% CI) versus 3.0 μg/d (R:1.00, 95% CI) decreased the risk/alcohol adjusted, smoking not (Boutron et al. 1996).
- 35.216 women, 216 colon cancers, 55-69 years of age/4 years of follow-up/<127 IU/d (R:1.00, 95% CI) versus >373 IU/d (0.77, 0.55-1.16) reduced the risk/alcohol adjusted but smoking not (Bostick et al. 1993)
- 46.771 men, 75.427 women, 38-75 years of age/16 years of follow up/≥600 IU/d (0.59, 0.40-0.88, 95% CI) and 450-599 IU/d (0.56, 0.36-0.87, 95% CI) versus 300-449 IU/d (0.57, 0.40-0.83, 95 % CI) and <150/d (R:1.00, 95% CI) decreased the risk of pancreatic cancer/smoking adjusted, alcohol not (Skinner et al. 2006)
- 47.935 male, 203 colon cancers, 40-75 years of age/ 6 years of follow up/>550IU/d (0.42, 0.19-0.91) versus <120 IU/d (0.88, 0.54-1.42) decreased the risk/smoking and alcohol adjusted (Kearney et al. 1996)
- 34702 women, 1998 rectal cancers, ≥55 years of age/9 years of follow up/>476 IU/d vitamin D intake (0.76, 0.50-1.16) versus <224 IU/d (R:1.00, 95% CI) decreased the risk /smoking adjusted, alcohol not (Zheng et al. 1998)
- 1294 men with prostate cancer, 1451 control, 46-74 years of age/11 years of follow up/ >4.05 μg/d vit D intake (1.32, 1.01-1.75) versus ≤1.98 μg/d (R:1.00, 95% CI) did not make any effect/smoking and alcohol adjusted (Tavani et al. 2005)
- 568 men and women, 40-80 years of age/1 year of follow up/ 26.9 ng/mL serum 25(OH)D (0.97, 0.62-1.52, 95% CI) versus 20.5 ng/mL as the lowest serum 25(OH)D (R:1.00, 95% CI) concentration in men and 17. 3 ng/mL serum 25(OH)D (0.49, 0.25-0.97) versus <17.2 ng/mL (R:1.00, 95% CI) decreased the

risk of colorectal adenoma/ alcohol adjusted but smoking not (Jacobs et al. 2007).

- 60866 men, 66883 women, 683 colorectal cancers, 50-74 years of age/ 5 years of follow up/≥240 IU daily vitamin D intake (0.74, 0.50-1.11, 95% CI) versus < 90 IU (R:1.00, 95 % CI) decreased the risk/alcohol and smoking not adjusted (McCullough et al. 2003).
- 118597 men, 575 pancreatic cancer, 43-70 years of age/>288 IU/d dietary vitamin D intake (0.71, 0.38-1.30, 95% CI) versus <288 IU/d (0.34, 0.17-0.67, 95%) decreased the risk/smoking adjusted, alcohol not (Bao et al. 2010)
- 3223 men and women with nonmelanoma skin cancer, 55-75 years of age/12 years of follow up/≥31 (1.6, 1.1-2.3, 95% CI) ng/ mLserum 25-Hydroxyvitamin D concentration as the highest quartile versus <19 ng/mL(R: 1.00, 95% CI) increased the risk/ alcohol and smoking not adjusted (Eide et al. 2011).
- 6937 men and women, 122 lung cancer, 36-49 years of age/24 years of follow up/ 131.3 nmol/L 25(OH)D serum concentration in women (0.16, 0.04-0.59, 95% CI) versus 47.3 nmol/L 25(OH) D serum concentration (0.72, 0.43-1.19, 95% CI) decreased the risk/ smoking and alcohol adjusted(Kilkkinen et al. 2008)
- 1295 postmenopausal breast cancer, 50-74 years of age/5.8 years of age/≥55 nmol/L (1.55, 1.00-2.39) as the highest serum 25(OH) D concentration versus to 10 nmol/L (1.14, 1.05-1.24) as the lowest serum 25(OH)D concentration decreased the risk/alcohol and smoking not adjusted) (Vrieling et al. 2011).
- 678 controls, 348 colon cancers, 164 rectal cancers, 65-74 years of age/≥557 IU/d vitamin D intake (0.8, 0.5-1.5, 95% CI) versus <148 IU/d (R:1.00, 95% CI) decreased the risk of rectal and colon cancers/alcohol adjusted, smoking not (Marcus and Newcomb, 1998).

QUERCETIN

The antioxidant flavonoid is in either glycoside or in aglycone form while most of the dietary intake is in the glycolside form. Sugar moieties can be released from quercetin glycosides following chewing, digestion and absorption. Small intestine, the kidneys, the large intestine and the liver rises the glucuronidated, methylated and sulfated forms of the flavonoid in addition to the quercetin (such as aglycone) which exists in plasma (D'Andrea et al. 2015). The richest sources are; caper, onion, cocoa powder, cranberries, cherries, green tea, black tea, broccoli (Nutrient Data Lab. USDA, 2007), lettuce, asparagus, green pepper, tomatoe, Romaine lettuce, whortleberry, lingonberry, cranberry, chokeberry, sweet rowan, rowanberry, billbery, strawberry and kale (Nishimuro et al. 2015; Hakkinen et al. 1999).

The chemical structure of pure quercetin is an unconjugated aglycone without any carbohydrate moiety. But, the form of the flavonoid in foods is in glycoside form while the supplemental forms are usually aglycone. Although both forms are readily bioavailable, glycoside forms have better absorption than agylycone (Edwards et al. 2007; Manach et al. 2005; Olthof et al. 2000).

One of the most exciting and crucial attributes of the flavonoid in cancer nutrition is that the flavonoid is converted into one of its antioxidant and anticancerogen isorhamnetin (Antunes-Ricardo et al. 2014; Kim et al. 2011) which can protect against an anticancer antibiotic, doxorubicin, induced cardiotoxicity (Sun et al. 2013).

The flavonoid has a phenolic hydroxyl group in its chemical structure and this property is essential for its anti-oxidant effect, by scavenging free radicals, e.g. superoxide anions (O2-), perhydroxyl radicals. (HOO) and chain-propagating lipid peroxy radicals (LOO). The number and the position of the hydroxyl groups dramatically affect the anti-oxidant capacity (Murakami et al. 2008). On the other hand, the flavonoid itself may undergo autooxidation (Canada et al. 1990). Briefly, like all the others, though the flavonoid is an antioxidant, it can generate ROS by autooxidation and redox-cycling (Gaspar et al. 1994).

One reason for the pro-oxidant effect of the flavonoid may be its inhibitory effect on the expression of the important antioxidants; manganese peroxidase and copper zinc peroxide dismutase (CuZn-SOD)mRNA) (Chang et al. 2006).The other reason, like all the other flavonoids and vitamins, quercetin produces its own radicals (quercetin radicals) after peroxidase-catalyzed oxidation in order to scavenge reactive peroxyl radicals (Jeong et al. 2009). The quercetin radicals during the administration of ROS inducing anti-cancer drugs, can increase the total ROS concentration to kill the cancer cells. Therefore, the anticancer drugs which produce ROS to kill cancer cells; sunitinib, sorafenib, tetrandrine, cisplatin, bortezomib, vorinostat, MG-132, metformin, thapsigargin, tunicamycin, 17AAG, DBeQ, ritonavir and brefeldin A, may have stronger anticancer potential if they are administered with an anticancer diet that involves quercetin rich foods; caper, onion, cocoa powder, cranberries, cherries, green tea, black tea, broccoli, lettuce, asparagus, green pepper, tomatoe, Romaine lettuce, whortleberry, lingonberry, cranberry, chokeberry, sweet rowan, rowanberry, billbery, strawberry and kale, creating a synergy via the induction of ROS. Confirming the ROS inducing ability, the quercetin radicals fragment nuclei, decrease mitochondrial membrane potential, activate caspase-3 and caspase-7 (the enzymes that permeabilize the mitochondrial membrane and subsequently causes ROS influx from the inner part of cytoplasm out of the membrane, increase caspase-3 and -9 activities and degrade ADP-ribose polymerase protein, the protein to repair DNA and program cell death) (Kim et al. 2013; Niu et al. 2011; Granado-Serrano et al. 2006; Liang et al. 2011). Therefore, the anticancer effect of the following anticancer drugs which induce caspase activity, followed by permeabilizing the mitochondrial membrane and inducing ROS influx, namely; costunolide (the stem bark of *Magnolia sieboldii*, a sesquiterpene lactone) (Kanno et al. 2008), mitomycin c (Pirnia et al. 2002), cisplatin (Kaushal et al. 2001), garcinol (Pan et al. 2001), brefeldin A (Lee et al. 2013), valinomycin (Abdalah et al. 2006), piceatannol (Kim et al. 2008), kinetin riboside (Dudzik et al. 2011), lipase inhibitor, THL (tetrahydrolipstatin) (Yao et al. 2011), imiquimod (Schon et al. 2003), SC560 (Lampiasi et al. 2006), romidepsin (Hanker et al. 2009), ouabain, digoxin, proscillaridin A (Winnicka et al. 2007),

borrelidin (Kawamura et al. 2003), sanguinarine, bortezomib (Larsson et al. 2010) MT-21(Watabe et al. 2000), ionidamine (as combined with radiation) (Miyato et al. 2004), K858 (Nakai et al. 2009), saikosaponin A (a triterpene saponin derived from *Bupleurum falcatum L.*) (Kim and Hong 2011), CIL-102 (Huang et al. 2005) and prodigiosin (Montaner and Perez-Tomas 2002) may exhibit more anticancerogenic potential if they are administered during quercetin rich nutrition since the flavonoid may form a synergy to activate caspase like the mentioned anticancer drugs, if a diet rich from the flavonoid rich foods; caper, onion, cocoa powder, cranberries, cherries, green tea, black tea, broccoli, lettuce, asparagus, green pepper, tomatoe, Romaine lettuce, whortleberry, lingonberry, cranberry, chokeberry, sweet rowan, rowanberry, billbery, strawberry and kale, are included into the treatment period, increasing the effect of the mentioned anticancer drugs via the induction of caspase activity.

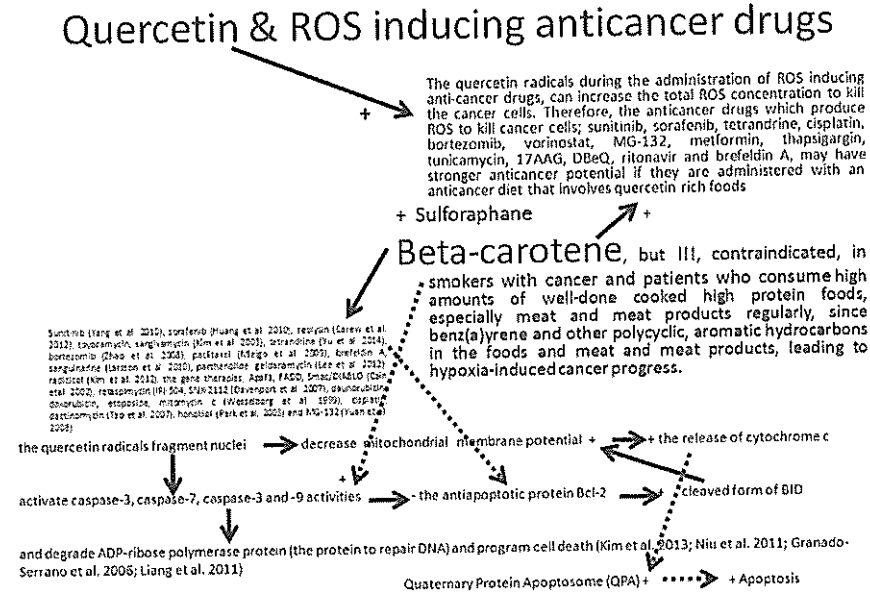


FIGURE 20

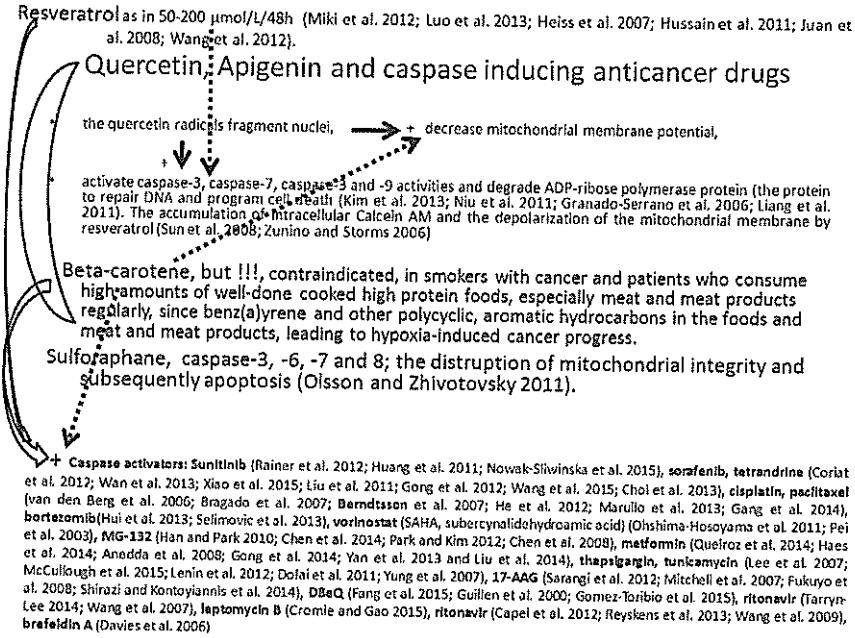


FIGURE 21

Quercetin's one of the anticancer effects may be due to its inhibitory effect on the expression of COX-2 (Cyclooxygenase-2), the enzyme which produces inflammatory and cancerogenic hormones (Xiao et al. 2011; D'mello et al. 2011, O'Leary et al. 2004) when it is administered at ≥1µM concentrations (Cheong et al. 2004). The inhibitory effect of the flavonoid on COX-2 may enhance the anticancer potential of the anticancer drugs which inhibit COX; celecoxib, magnolol, honokiol, eugenol, bis-eugenol, tetrandrine, 17AAG, raloxifene, rofecoxib, nafroxen, dexamethasone, hydrocortisone, triamcinolone acetonide, methyl prednisolone and beclomethasone diproprionate, if an anticancer diet rich in the flavonoid is followed during the treatments with the mentioned drugs, since the flavonoid and the anticancer drugs may show a synergy to inhibit COX-2.

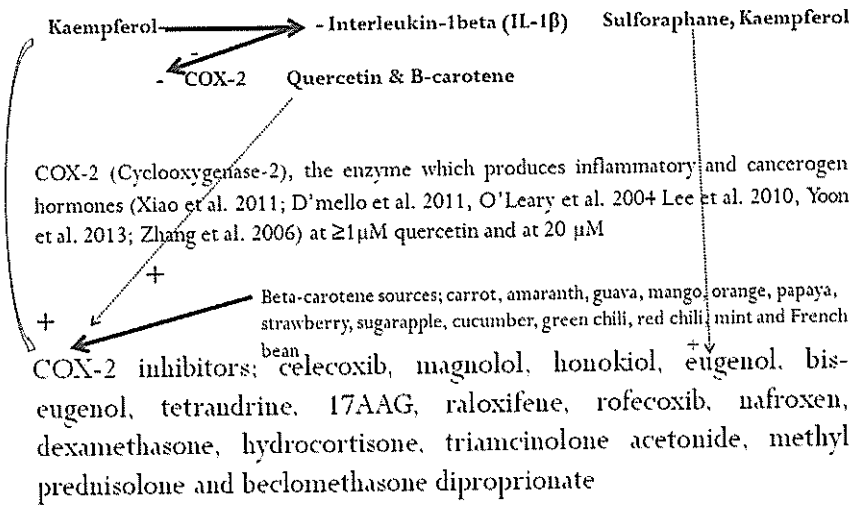


FIGURE 22

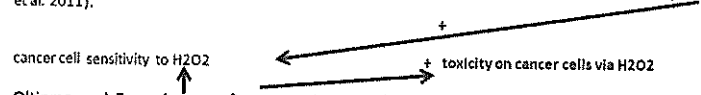
The flavonoid's one of the important anticancer effects may be related with tumor suppressor gene, p38, and the anti-oxidant phase II enzyme, Nrf2 which reduces the toxicity of the toxic and cancerogenic compounds by increasing their solubility. The flavonoid (50 μM) first induces a time-dependent activation of p38 which then results in the stimulation of Nrf2 (Granado-Serrano et al. 2012; Lee et al. 2015). Thioredoxin-dependent peroxide reductases, (PRDX3, PRDX5, Nrf1), the mitochondrial enzymes which are antioxidant like Nrf2, are also induced by the flavonoid which may be important in cancer prevention (Miyamoto et al. 2011). The activation of the expression of PRDX3, PRDX5 and Nrf1 is crucial, especially in the anticancer potential of the flavonoid and in chemotherapy because the upregulation of Nrf1, PRDX3 and PRDX5 renders the cells sensitive to hydrogen peroxide and thus, the downregulation of these enzymes may not be desired in anticancer treatments and may be contraindicated which administer chemotherapeutic agents that target cancer cells by producing H_2O_2. Though, there seems no study as related to the effects of the anticancer drugs on H_2O_2, the only current chemotherapeutic agents which produce H_2O_2 at high concentrations appear as; curcumin, epigallocatechin

gallate, beta-caroten, sulforaphane, capsaicin and vitamin C (Kawanishi et al. 2005; Ito et al. 2004). Therefore, during the treatments with the high doses of the mentioned chemotherapeutic agents; curcumin, epigallocatechin gallate, beta-caroten, sulforaphane, capsaicin and vitamin C, the curcumin rich foods/plants, e.g. *Curcuma langa*, cinnamon, cinnamon containing foods, epigallocatechin gallate rich plants, e.g. green tea and black tea, beta karoten rich foods, e.g.; carrot, amaranth, guava, mango, orange, papaya, spinach, tomato, lettuce, cucumber, green chili, red chili, mint and French bean, vitamin C rich foods, e.g. red pepper, orange, green pepper, broccoli, strawberries, Brussels sprouts, tomato juice, tomato, cantaloupe, cabbage, cauliflower, potato, spinach, green peas, green leafy, citrose fruits, sulforaphane rich foods, e.g. white cabbage, broccoli, red cabbage, cauliflower, Brussels sprouts, radish, mustard, turnip and Chinese kale and capsaicin, e.g. hot chili peppers in the anti-cancer diet, may improve the anticancer potential of the each chemotherapeutic agents since these foods may increase H_2O_2 level to kill cancer cells, in addition to the H_2O_2 produced by the mentioned agents.

Tumor suppressor gene, p38, H2O2, and the anti-oxidant phase II enzymes; Nrf2, PRDX3, PRDX5, Nrf1 and Quercetin

The flavonoid (50 μM) first induces a time-dependent activation of p38 which then results in the stimulation of Nrf2 (Granado-Serrano et al. 2012; Lee et al. 2015).

The upregulation of thioredoxin-dependent peroxide reductases (PRDX3, PRDX5, Nrf1) expressions by quercetin, curcumin, epigallocatechin gallate, beta-caroten, sulforaphane, capsaicin and vitamin C (Kawanishi et al. 2005; Ito et al. 2004; Miyamoto et al. 2011).



Oltipraz and Zerumbone → +curcumin, epigallocatechin gallate, beta-caroten, sulforaphane, capsaicin and vitamin C, the curcumin rich foods/plants, e.g; Curcuma langa, cinnamon, cinnamon containing foods, epigallocatechin gallate rich plants, e.g; green tea and black tea, beta karoten rich foods, e.g.; carrot, amaranth, guava, mango, orange, papaya, spinach, tomato, lettuce, cucumber, green chili, red chili, mint and French bean, vitamin C rich foods, e.g.; red pepper, orange, green pepper, broccoli, strawberries, Brussels sprouts, tomato juice, tomato, cantaloupe, cabbage, cauliflower, potato, spinach, green peas, green leafy, citrose fruits, sulforaphane rich foods, e.g. ; white cabbage, broccoli, red cabbage, cauliflower, Brussels sprouts, radish, mustard, turnip and Chinese kale and capsaicin, e.g.; hot chili peppers, quercetin rich foods; caper, onion, cocoa powder, cranberries, cherries, green tea, black tea, broccoli, lettuce, asparagus, green pepper, tomatoe, Romaine lettuce, whortleberry, lingonberry, cranberry, chokeberry, sweet rowan, rowanberry, billbery, strawberry and kale, Zeaxanthin; egg yolk, maize (corn), red seedless grape, zucchini squash, orange pepper, cucumber, green pepper, orange juice, honeydew, celery, green grapes, Brussel sprouts, orange, mango, tomato juice and peach (Sommerburg et al. 1998), ginger (which contains 6-DG), in the anti-cancer diet, may improve the anticancer potential of the each chemotherapeutic agents since these foods may increase H2O2 level to kill cancer cells, in addition to the H2O2 produced by the mentioned agents.

But, Oltipraz, Zerumbone and sulforaphane X caspase & ROS inducers !!!

FIGURE 23

The inhibition of GRP78, the central regulator of endoplasmic reticulum (ER) and the chaperon which controls ER with its protein folding capacity, by quercetin (Li et al. 2009), may be another factor which may contribute to the anticancer effect of the flavonoid. Such effect depolarizes the membrane of ER and induces a ROS influx and subsequently activation of caspases. However, the inhibitory effect on GRP78 and the subsequent inhibition of β-catenin signaling by the flavonoid may enhance the anticancer potential of the anticancer drugs; sunitinib, sorafenib, SCH727965, metformin and bortezomib combination, tunicamycin, radicicol, KUSs, versipeolstatin, pyrivinium pamoate, tanespimycin and 17-AAG, the drugs all of which target cancer cells by inhibiting the chaperon and β-catenin signaling, like the flavonoid.

Wnt signaling are the signal transduction which are made of proteins that pass signals from outside of a cell through cell surface receptors to the inside of the cell. The signaling results in the accumulation of beta-catenin (Morin 1999). The degradation of the accumulated protein, beta-catenin, is initiated upon amino-terminal serine/threonine phosphorylation which is performed by glycogen synthase kinase-3 (GSK-3) as in complex with tumor suppressor proteins, Axin-associated kinases (Liu et al. 2002). The subsequent deregulation of beta-catenin signaling is always associated with the formation and progress of malignancies (Morin 1999). On the other hand, GRP78 enhances β-catenin signaling (Li et al. 2014).

Erbb2 (Receptor tyrosine-protein kinase also known as human epidermal growth factor receptor 2, HER2) is a glycoprotein, proto-oncogene and a member of the human epidermal growth factor receptor family, whose overexpression plays important role in the development and progression of certain aggressive types of breast cancer (Johnson et al. 2010). On the other hand, quercetin (50-100 μM/L) inhibits cell growth and induces apoptosis by its ability to down-regulate Erbb2/Erbb3 signaling (Kim et al. 2005; Jeong et al. 2008). The inhibition of ErbB2 (HER2) appears as one of the novel anticancer strategies, currently. The following anticancer drugs whose anticancer potentials

by inhibiting ErbB2 are confirmed by the following references in parentheses; Lapatinib (GW-572016) ditosylate (Chu et al. 2005), afatinib (Nelson et al. 2013), neratinib (Burstein et al. 2010), canertinib (Allen et al. 2002), CP-724714 (Jani et al. 2007), sapatinib (AZD8931) (Hickinson et al. 2010), AC480 (BMS-599626) (Schroeder et al. 2014), TAK-285 (Nakayama et al. 2013), CUDC-101 (Galloway et al. 2015), AEE788 (Traxler et al. 2004), tyrphostin AG879, tyrphostin AG825 (Lee et al. 2008), mubritinib (TAK 165) (Nagasawa et al. 2006), SKLB1206 (Pan et al. 2012), sorafenib (Martinelli et al. 2010), trastuzumab and saracatinib (Han et al. 2014), may show greater anticancer effects if they are administered during an anticancer diet rich in quercetin since quercetin inhibits ErbB2 and thus, may form a synergy with the mentioned anticancer drugs which similarly inhibit the glycoprotein.

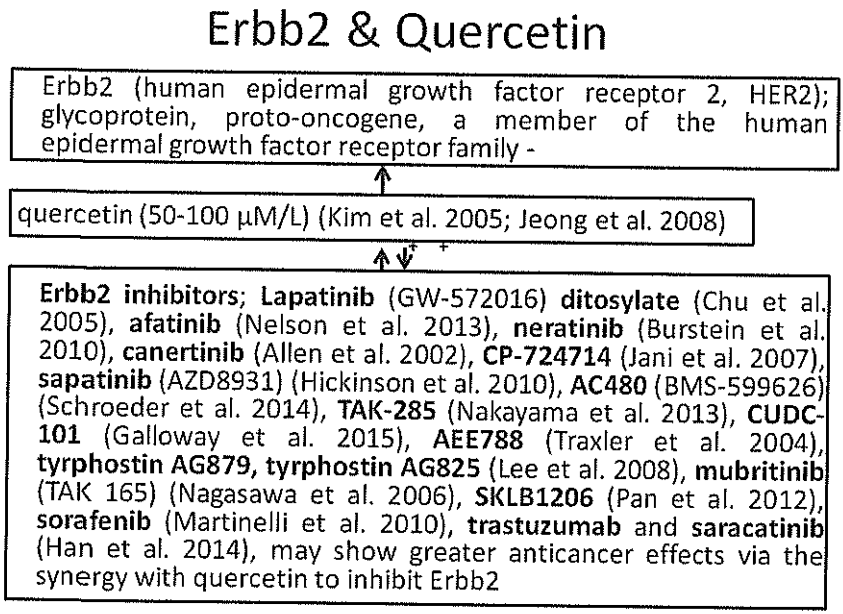


FIGURE 24

The effect of the flavonoid on Hedgehog (Hh) signaling, the signaling which transmits information to embryonic cells for the cell development and survival, is unclear since the findings of the very limited number

of studies (Li et al. 2014; Slusarz et al. 2010) are conflicted. Therefore, until the effect of the flavonoid on the signaling becomes clear, it may be safer to avoid quercetin rich foods during the treatments with the Hh inhibitors; SANT1-SANT4, CUR-61414, HhAntag-691, GDC-0449, guggulsterone, saridegib, phthaladines, itracanozole, NVP-LDE225, TAK-441, XL-139, HTS piperidines, MRT-92, MRT-83, PF-04449913, N-acylethanolamides, 2-acylglycerols and 2-alkylglycerol.

Notch (DSL) proteins are a family of transmembrane proteins. Notch interaction with its cell-bound ligands establishes an intercellular signaling (Notch signaling) pathway which plays a key role in the development of angiogenesis (Liu et al. 2003), expansion of the hematopoietic stem cells, the blood cells which locate in the red bone marrow and give rise to all the other blood cells (Nobta et al. 2005). Although Notch-1 functions as a tumor suppressor under normal conditions, the inappropriate activation and deregulation of the signaling stimulate proliferation and prevent apoptolsis in lymphoblastic leukemia, breast cancer, melanoma and adenocarcinoma (Roy et al. 2007; Dickson et al. 2007; Reedijk et al. 2005; Pinnix and Herlyn 2007). Because of the mentioned activation and deregulation of the Notch signaling, Notch inhibitors have currently appeared as a promising new approach in cancer treatment (Purow 2012; Brennan and Clarke 2013; Aster and Blacklow 2012). OMP-59R5 anti-Notch2/3 mAb (Yen et al. 2015), NRR1 anti-Notch1 mAb (Wu et al. 2010), NRR2 anti-Notch2 mAb (Falk et al. 2012), NRR3 anti-Notch2 mAb (Teodorczyk and Schmidt 2015), OMP-21M18 anti-DLL4 mAb (Yan 2011), DLL1-Fc and JAG1-Fc Anti-Delta-like 1 and Jagged 1 Fc chimeric mAbs (Huang et al. 2011; Urs et al. 2012), A5622A Anti-nicastrin mAb (Filipovic et al. 2014), RO4929097 (Debeb et al. 2012), MRK-003 (Mizuma et al. 2012), MRK-0752 (Krop et al. 2012), PF-03084014 (Lopez-Guerra et al. 2015), MAM peptide antagonist and SAHM1 (Moellering et al. 2009) are the current novel anti-cancer agents which kill cancer cells by targeting Notch. Not only the mentioned Notch inhibitors but also genistein, sulforaphane and resveratrol are the food and plant origin bio-active compounds which kill tumor cells by targeting Notch, like quercetin (Xia et al. 2012; Li et al. 2012, Zhang et al. 2014; Wang et al. 2011). Therefore, genistein rich foods; soy bean, fava bean, kudzu,

lupine, psoralea and miso, sulphoraphane rich foods; white cabbage, broccoli, red cabbage, cauliflower, Brussels sprouts, radish, mustard, turnip and Chinese kale, curcumin rich foods/plants; cinnamon and *Curcuma longa*, resveratrol rich foods; berries, peanuts and grapes and quercetin rich foods; black tea, green tea, red leaf, tomatoes, green pepper, asparagus, lettuce, cocoa, cranberries, cherries, onion, broccoli, apple, red grape and caper, may be useful to be included into the anticancer diet, especially during the treatments with the mentioned anticancer drugs, since the bio-active food/plant compounds and the anticancer drugs may form a synergy to inhibit Notch and thus, may show greater anticancer potential.

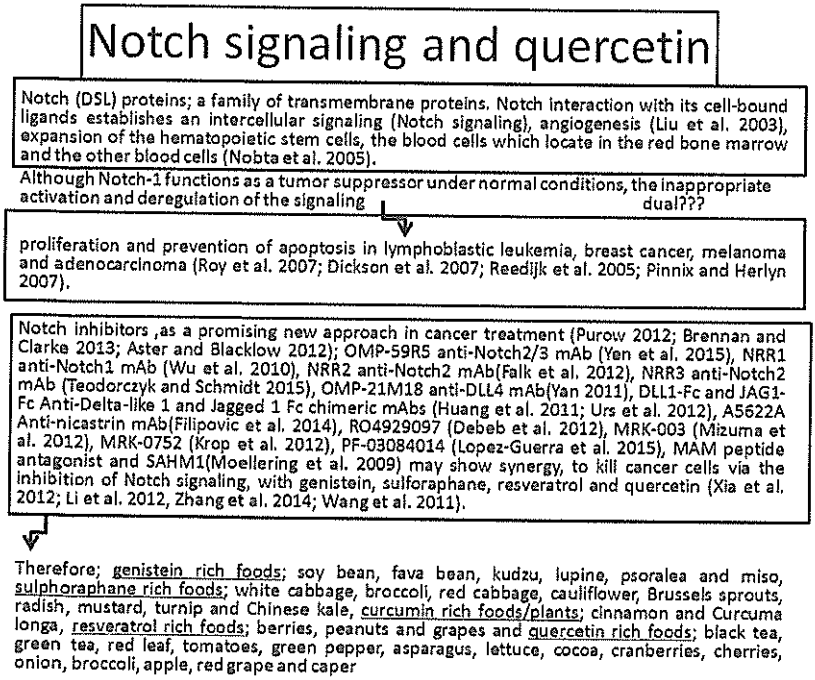


FIGURE 25

The flavonoid's one other anticancer effect may be due to its induction on p38, the mitogen-activated protein kinase which can inhibit cell growth by inhibiting the expression of cyclin D, while the flavonoid also triggers p38/MAPK signaling, the signaling which

mediates the mitochondria induced apoptosis stemming from the release of cytochrome c (Liu et al. 2014). This ability of the flavonoid may enhance the anticancer potential of the anticancer agents; cisplatin, transplatin, platinum (IV) chloride, brefeldin A, thapsigargin, tunicamycin, tamoxifen, betulinic acid, honokiol, bortezomib, 4-phenyl-3-betulinic acid (PBA), vorinostat, geldanamycin, raloxifen, paclitaxel and panaxydol, the drugs all of which activate p38 and p38MAPK signaling, like the flavonoid and unlike vitamin C as previously mentioned. But, under some conditions which depend on the type of stimuli or the cellular contexts that are still remain to be unknown, p38 may be exploited by the cancer cells to grow and proliferate and hence, p38 inhibitors, namely; doramapimod (BIRB796), VX-745, VX-702, AMG-548, Scio-323, Scio-469 and pamapimod (R04402257) have also been administered as another anticancer approach. Unlike vitamin C and vitamin C rich foods; quercetin and quercetin rich foods may decrease the anticancer potentials of the treatments using these p38 inhibitors since the flavonoid induces p38, as in contrast with these inhibitors.

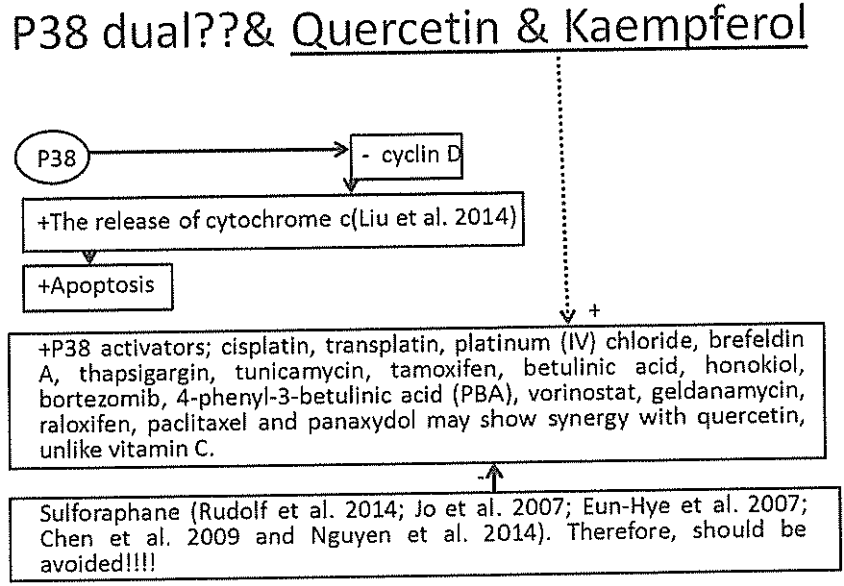
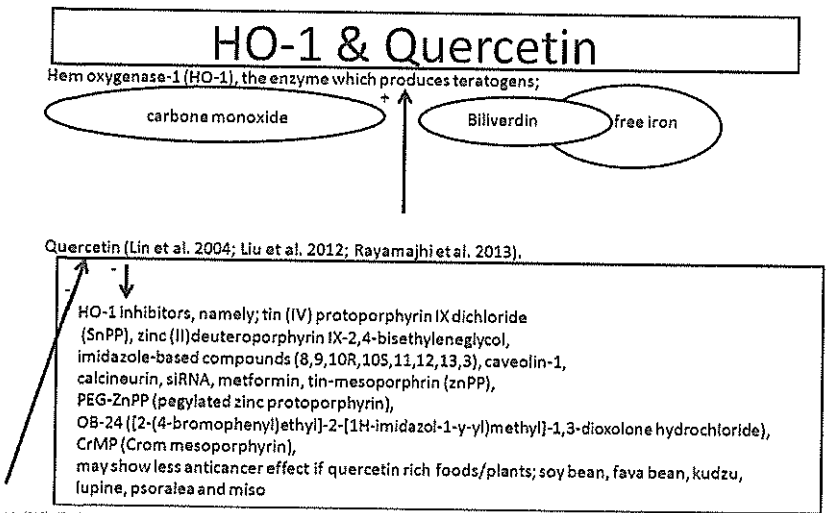


FIGURE 26

Hem oxygenase-1 (HO-1), the enzyme which produces teratogens; carbone monoxide, biliverdin and free iron, is induced by the flavonoid (Lin et al. 2004; Liu et al. 2012; Rayamajhi et al. 2013). Therefore, the anticancer agents which target (HO-1) inhibition (that the inhibition is especially important for the patients or the people who consume rich amounts of iron and animal origin foods) with the HO-1 inhibitors, namely; tin (IV) protoporphyrin IX dichloride (SnPP), zinc (II) deuteroporphyrin IX-2,4-bisethyleneglycol, imidazole-based compounds (8,9,10R,10S,11,12,13,3), caveolin-1, calcineurin, siRNA, metformin, tin-mesoporphrin (znPP), PEG-ZnPP (pegylated zinc protoporphyrin), OB-24 ([2-(4-bromophenyl)ethyl]-2-[1H-imidazol-1-y-yl)methyl]-1,3-dioxolone hydrochloride), CrMP (Crom mesoporphyrin), may show less anticancer effect if quercetin rich foods/plants; soy bean, fava bean, kudzu, lupine, psoralea and miso are consumed or supplemented during the treatments with these anticancer agents since quercetin may be contraindicated with the anticancer agents, by inducing HO-1 activity.



capsaicin (CAP), dihydrocapsaicin (DHC, the major pungent components of hot peppers)(Kim and Lee 2014). enterolactone, a mammalian lignin and the plant lignans which can produce enterolactone such as secoisolariciresinol diglucoside, the richest sources; flaxseed, sunflower sesame and pumpkin seeds (Strandas et al. 2008; Kivela et al. 2008), matairesinol (whole grains) (Kenneyer et al. 2003), lariciresinol (Brassica vegetables like Brussel sprouts and broccoli), pinoresinol (sesame and Brassica vegetables) (Mulder et al. foods, white cabbage, Brussel sprouts, radish, mustard, cauliflower, turnip and Chinese kale, arginine rich foods, turkey breast, beef, ground meat, (2005).esculetin and coumarin (red clover, cinnamon)(Eeilin and Sorensen 2014, Kim et al. 2014, Booth et al. 2006) and finally sulforaphane and sulforaphane rich upin, soybean, nuts, seeds. egg white, peanut, mollusk, chickpea, soy flour, sesame seed, fentil, beans, chicken meat and pork meat and geniplin (Gardenia fruit) (Potusek et al. 2011), the foods most of which also contain plant lignans that produce enterolactone (Lee and Lee 2011, Keumet al. 2006)

FIGURE 27

According to the only study carried out by Huang et al. (2013) about FOXO3 and quercetin association, FOXO3, the gene and transcription factor which triggers apoptosis through the upregulation of other apoptotic genes like Bim and PUMA, is activated by the flavonoid. So, the treatments with the FOXO3 activators like; metformin, doxorubicin, nipradilol, timolol, melatonin, withaferin A, bortezomib, vorinostat, tunicamycin, paclitaxel, geldanamycin, AZD5363, cisplatin and 5-aza-2-deoxycytidine, may benefit from the involvement of the quercetin and quercetin rich foods/plants, e. g. soy bean, fava bean, kudzu, lupine, psoralea and miso, into the anticancer diet since the flavonoid and the mentioned anticancer agents may form a synergy to activate FOXO3.

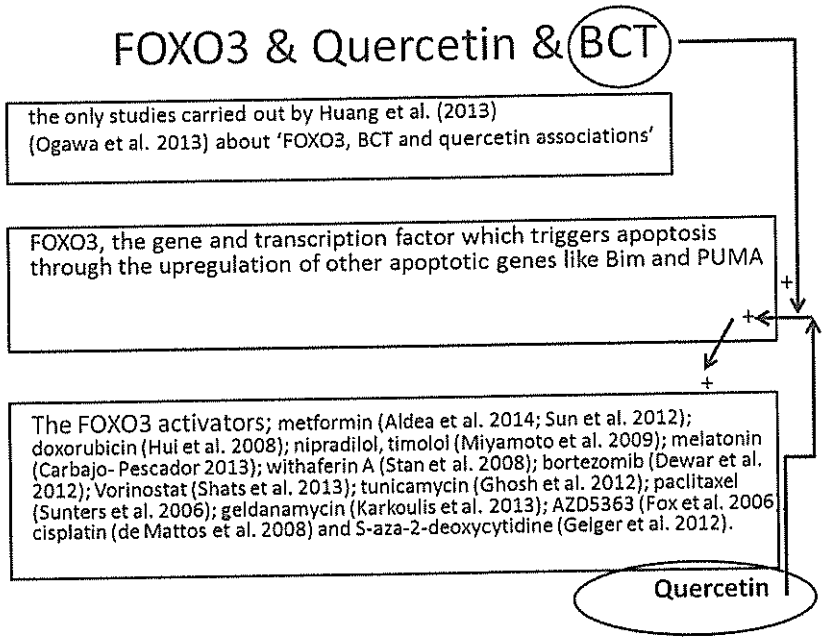


FIGURE 28

The MAPK/ERK signaling, the binding of the signaling molecule to the receptor on cell surface and the protein expression by DNA which starts cell division and the association of the signaling with the flavonoid is still unclear. Pan et al. (2015) and Nguyen et al. (2004) inform the

inhibitory effect of the flavonoid on the signaling but Nam et al. (2008) claim the opposite.

The protein, Nrf2, which controls the production of most of the phase II enzymes and increases the solubility of the toxic and cancerogen compounds to reduce their toxicity, is upregulated and its level is increased by the flavonoid (Lee et al. 2015; Lee et al. 2011; Alrawaiq and Abdullah 2014; Miyamoto et al. 2010). Nrf2 regulates the constitutive and inducible transcription of a wide array of genes which are involved in drug metabolism, detoxification and antioxidant defenses. The protein is sequestered in the cytoplasm by another protein known as Keap 1. In response to oxidative stress, Keap 1-mediated ubiquitination of Nrf2 is decreased and as a result Nrf2 is activated. Briefly, without the response to the oxidative stress, Keap 1 repress Nrf2. Residues C273 and C288 at the intervening region domain of Keap 1 are responsible for the repression of Nrf2 by Keap 1. Therefore, some novel Nrf2 inducers; BM31, BM10 and BM40 have been invented to target these residues (the currently discovered ones are C273, C288 and C297) which repress Nrf2 and which are located in the intervening region domain of Keap 1 (Aleksunes and Manautou 2007; Wu et al. 2010). These Nrf2 inducers also upregulate the expression of ARE-regulated enyme gamma-glutamylcysteine synthetase, a key regulatory enzyme in the synthesis of the antioxidant protein, glutathione (Soltaninassab et al. 2000). The other Nrf2 inducers are 2-cyano-3,12-dioxooleana-1,9-dien-28-oic acid-methyl amide (CDDO-MA), tBHQ, 3H-1,2-dithiole-3-thione, sulforaphane (Williamson et al. 2012), tanshinone 1 and dihydrotanshino (Tao et al. 2013), BHA (Butyl hydroxyanisol), ethoxyquin and I3C (Indol-3-carbinol) (Kwak et al. 2004). Unfortunately, the protection against cancer by the use of Nrf2 inducers and Nrf2 inducing flavonoids like quercetin is another dilemma which requires further studies to be highlighted. Because, there are important findings which claim that Nrf2 induction may not only increase the defence of the healthy cells to oxidation but may also enhance the resistance of cancer cells to chemotherapeutic drugs; cisplatin, doxorubicin and etoposide (Wang et al. 2008). Although, the reason for the enhancement in the defence mechanism and resistance of cancer cells to the chemotherapeutic drugs is not clear, what seems obvious is that, Nrf2 may increase the

resistance of the cells against oxidation via the prevention of ROS production. Confirmingly, Raj et al. (2011) have identified the small molecule, piperlongumine, a natural product isolated from the Long pepper (*Pipier longum*) which selectively blocks Nrf2-Keap 1, sparing normal cells from the toxicity of ROS. These researchers hypothesize that malignantly transformed cells have a higher capacity to generate ROS and thus they often need protection by Nrf2-Keap 1, from the excess amount of ROS which they and some of the anticancer drugs produce. Although Nrf2 acts as a pro-oxidant under some conditions by increasing ROS production (Kovac et al. 2015), during the treatments with the anticancer drugs which target cancer cells by producing ROS, like cancer cells, cancer cells may have needed the defence by Nrf2-Keap 1 and may have benefited from the anti-oxidant defence of Nrf2-Keap 1 to be protected from ROS. As a result, their resistance to the anticancer drugs may have been enhanced. The enhancement in the resistance of cancer cells to the anticancer drugs as a result of the protection of cancer cells by Nrf2, from ROS which come from both cancer cells and anticancer drug, should be considered as the dark side of the protein. Briefly, treatments with Nrf2 inducers with or without anticancer diet, involving Nrf2 inducing flavonoids like quercetin, sulforaphane and I3C, still continue to be a dilemma and thus, urgently need new studies to be highlighted. Especially, the two faced character of Nrf2, sometimes being a pro-antioxidant, but the other times being an antioxidant under some conditions and the questions for 'what are these conditions which make the protein an antioxidant or a pro-oxidant', should first be answered to be able to continue and follow the anticancer treatments using Nrf2-Keap 1 inducers and the anticancer diet rich in Nrf2 inducing flavonoids like quercetin. Without finding answers for the mentioned questions, the status and efficiency of either the anticancer treatments or the flavonoids which induce Nrf2-Keap 1 pathway, will continue to be ambiguous.

One of the causative factors of cancer, the excess loas of iron in body, begins to form with transferring (TF), a protein which binds two atoms of ferric (Fe^{3}+) iron. TF-bound iron circulates in the bloodstream and reaches to tissues by binding to transferring receptor 1 (TFR1). The ferric iron in iron-TF-TFR1 complex is reduced to ferrous iron (Fe_{2}+) by

STEAP reductases. Divalent metal transporter (DMT1) then facilitates the penetration of ferrous iron from the cell into the pool of loosely iron. This iron in the pool is utilized for the conversion of ribonucleotides to deoxyribonucleotides, the synthesis of heme and iron-sulphur clusters while the excess of the iron is used for the oxidative phosphorylation and protein synthesis (Torti and Torti 2013). On the other hand, the accumulation of the ferrous form of iron which are converted from ferric form by STEAP reductases (STEAP1, STEAP2 and STEAP3) has been found closely related to cancer. Similary, the overexpression of the STEAP proteins has often been associated with cancer (Ohgami et al. 2005; Gomes et al. 2012; Grunewald et al. 2012). Like STEAP proteins, TFR1 is also highly expressed in breast cancer leukemia, lymphoma, bladder cancer, lung cancer and glioma (Daniels et al. 2012; Jeong et al. 2015). Based on the proliferative effects of STEAP proteins and TFR1 via the available ferrous form of iron supply from both these proteins and receptors, STEAP inhibitors and TFR1 antibodies have appeared as the novel cancer treatments which target iron metabolism, by blocking iron supply and ferrous form of iron formation and finally, the utilization of iron for cancer growth. The namely novel STEAP inhibitors and TFR binders; mouse IgG2akmAbs92.30, mouse IgG2akmAbs120.545 (Challita-Eid et al. 2007), mouse anti-TFR1 antibody, monoclonal [TFR-O1] (Callens et al. 2008), pectocin, M1 and M2 (Grinter et al. 2012), mouse Anti-TfR1 antibody, monoclonal [C2] (FITC) (Manich et al. 2013), mouse Anti-TfR1 antibody, Monoclonal antibody (Skikne 2008), ch128.1Av (Daniels et al. 2011), may have greater anticancer potential if quercetin rich foods; caper, onion, cocoa and cocoa powder, cranberries, cherries, green tea, black tea, broccoli, lettuce, asparagus, green pepper, berries, and kale, since the flavonoid is an iron chelator (Guo et al. 2007; Hajji et al. 2006). The flavonoid also inhibits iron absorption, binding iron between its 3-hydroxyl and 4-carbonyl groups. The methylation of the 3-hydroxyl group negates the increase in apical uptake of the mineral (Lesjak et al. 2014). It seems clear that, the flavonoid and flavonoid rich foods may be useful to enhance the anticancer potential of STEAP inhibitors and TFR binders by creating a synergy to bind iron, and further, the lifestyle which often prefers to consume iron rich foods (e.g.red meat and its products, fish meat, dark

green leafy vegetables..) in great amounts regularly, may benefit from the flavonoid. But, it should be noted that, the others like the people who make regular sport and body building exercises or the people with anemia or chronique fatique syndrome may adversely be affected since these the two mentioned groups may be suffered from iron deficiency and for these groups, heavy consumption of the flavonoid rich foods; caper, onion, cocoa and cocoa powder, cranberries, berries, kale, green tea, black tea, lettuce, asparagus, green pepper and kale may adversely affect them.

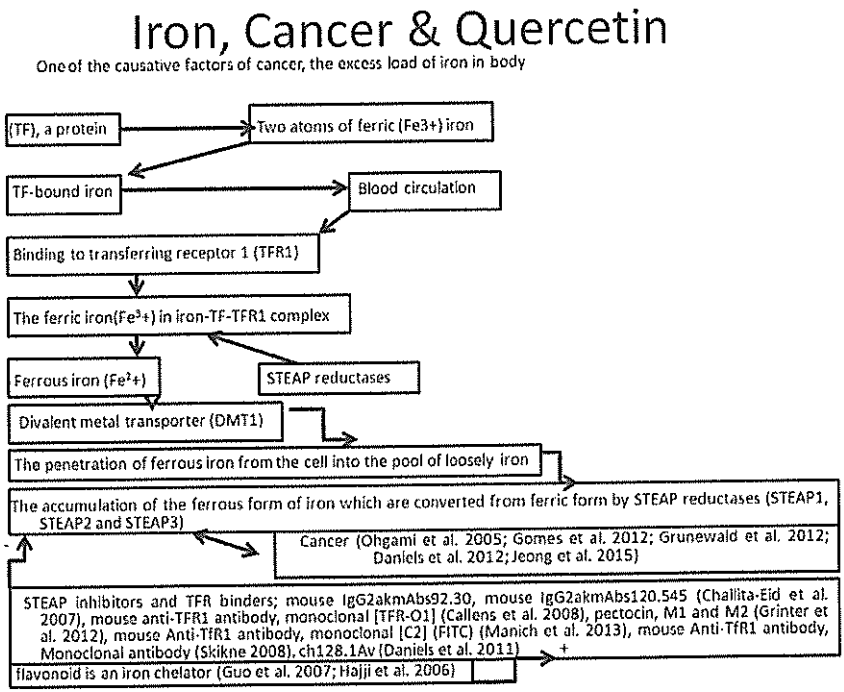


FIGURE 29

Quercetin also inhibits Vascular Endothelial Growth Factor (VEGF) (the signal protein to stimulate vasculogenesis, the process of blood vessel formation and angiogenesis) (Luo et al. 2008; Pratheeshkumar et al. 2012; Li et al. 2015) which may be an explanation for one of the anticancer effects of the flavonoid. Since the flavonoid has a significant inhibitory effect on VEGF, the anticancer potential of the anticancer drugs which

induce apoptosis and inhibit angiogenesis by inhibiting VEGF; sunitinib, sorafenib, bortezomib, bortezomib and MP0250 combination, MG132, MG262, KF58333, 17-AAG, geldanamycin A1, budesonide, brefeldin A, monensin, ritonavir, bevacizumab, ranibizumab, fulvestrant and vandetanib combination, tamoxifen, clomiphene, nafoxidine, ICI182780, metformin, paclitaxel, tunicamycin and PTK787/ZK222584 (Vatalanib) may be enhanced via their synergism to inhibit VEGF.

The flavonoid's another anticancer effect may be due to its inhibitory effect on NF-kB (nuclear factor kappa-light-chain enhancer of activated B cells), the protein which controls DNA transcription while it may stimulate cancer if it is extremely activated (Kang et al. 2013; Ruiz et al. 2007; Min et al. 2007). Therefore, the quercetin rich foods; caper, onion, cocoa and cocoa powder, cranberries, berries, kale, green tea, black tea, lettuce, asparagus, green pepper and kale in an anticancer diet may enhance the effects of anticancer drugs which similarly inhibit NF-kB, namely; emetine, fluorosalan, lestaurtinib, ectinascidin 743, chromomycin A3 and bortezomib. On the other hand, the flavonoid increases the activation of ERK and MEK 1/2, the signaling molecules which stimulate growth and proliferation, as in contrast with vitamin C and vitamin C rich foods and genistein and genistein rich foods, e. g. kudzu, soybean, favabean, lupine, psorolea, miso, banana, broccoli, fresh cabbage, grapefruit, fresh spinach, tomato, lettuce, citrose fruits, sulforaphane and sulforaphane rich foods, e.g.broccoli, fresh cabbage, radish, mustard, Brussels sprouts, cauliflower, Chinese kale and turnip and vorinostat, lapatinib, fulvestrant, PD98059, UO126 and honokiol, the vitamin, flavonoids and anticancer drugs, all of which inhibit MEK 1/2/ERK inhibitors and thus, the quercetin rich foods; caper, onion, cocoa and cocoa powder, cranberries, berries, kale, green tea, black tea, lettuce, asparagus, green pepper and kale may be advised to be avoided in the anticancer diet since quercetin may restrict the anticancer potential of the mentioned anticancer drugs, sulforaphane, genistein and vitamin C rich foods, by activating the signaling.

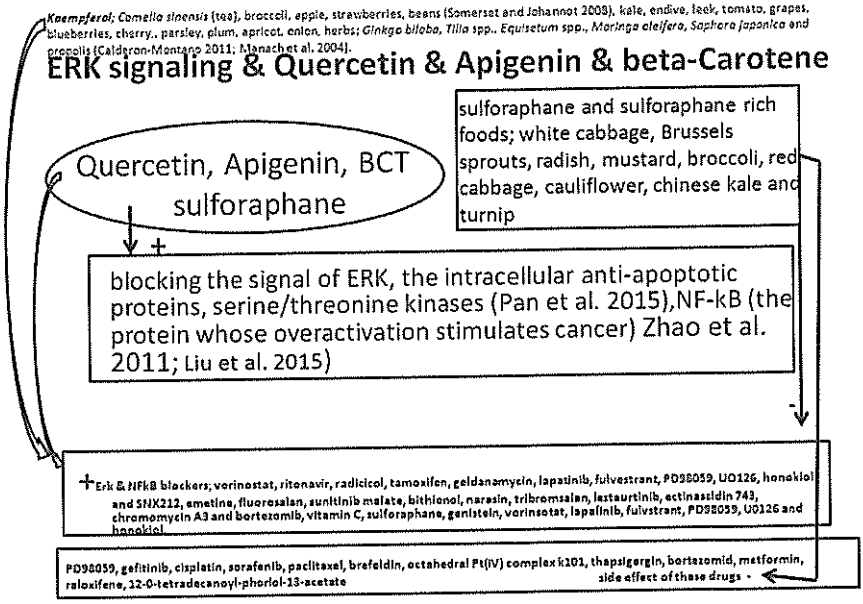


FIGURE 30

The effect of quercetin on the anti-apoptotic proteins; Cdc25A and Cdc25C is still unknown and waiting for the studies to be highlighted. Thus, the quercetin rich foods; caper, onion, cocoa and cocoa powder, cranberries, berries, kale, green tea, black tea, lettuce, asparagus, green pepper and kale should better be avoided in the diet during the treatments with Cdc25A and Cdc25C inhibitors; K252a, NSC663284, NSC95397, mpV, BN82002 and hexaprenylhydroquinone, until the effect of the flavonoid on the anti-apoptotic proteins is determined.

Bcl-xL (B-cell lymphoma-extra large), the transmembrane molecule in the mitochondria and a member of the Bcl-2 family of proteins, which prevents the release of mitochondrial contents such as cytochrom c (which induces apoptosis) has been informed to be decreased by the flavonoid (Granado-Serrano et al. 2006). Inhibition of Bcl-2 proteins including Bcl-xL by using small molecule inhibitors (SMI) has been appeared as one of the novel anticancer treatments. These antagonists aim to interfere with specific protein-protein interactions, compete with anti-apoptotic members of Bcl-2 protein family to occupy BH3

(the anti-apoptotic members of Bcl-2 proteins), docking grooves on the surfaces of antiapoptotic members of Bcl-2 protein family. Instead of directly initiating cell death, these inhibitors decrease apoptotic threshold in tumor cells that were already primed to death, less side effects unlike conventional chemo-radiotherapies. The namely novel anti-apoptotic Bcl-2 protein inhibitors, SMI, are e.g. HA14-1, TW-37 (Wang et al. 2015; Chen et al. 2002; Lickliter et al. 2003), AT-101 (Zerp et al. 2009), obatoclax (Goy et al. 2014), ABT-263 (Wang et al. 2014), ABT-737 (Klymenko et al. 2011), ABT-263 and ABT-199 (Brumatti and Ekert 2013), and the anticancer drugs that inhibit Bcl-2, e.g. sunitinib (Saito et al. 2012), sorafenib (Shimizu et al. 2010, thapsigargin (Wei et al. 1998), bortezomib (Mortenson et al. 2005), 17-AAG (Wang et al. 2014), vorinostat (Buglio et al. 2008), honokiol (Fan et al. 2014), metformin (Yang et al. 2014), tetrandrine (Liu et al. 2015), tamoxifen (Raha et al. 2015), geldanamycin, radicicol (Wu et al. 2013), raloxifen (Rossi et al. 2011; Wang et al. 2014). Since all the mentioned SMI, anticancer drugs and the flavonoid inhibit Bcl-2, their combined administrations rather than their sole applications, may yield greater anticancer potential. Hence, quercetin rich foods; caper, onion, cocoa and cocoa powder, cranberries, berries, kale, green tea, black tea, lettuce, asparagus, green pepper and kale, may be useful in the anticancer diet to form a synergy to maintain a much stronger Bcl-2 inhibition. It should be noted that the most important advantage of these protein molecules is that they increase the protein stability of Mcl-1 (the protein whose function is cellular processes and growth) and the inactivation of GSK-3β (Glycogen synthase kinase-3, an enzyme which is involved in energy metabolism, neuronal cell development and body pattern formation). Contrarily, chemo/radiotherapies induce apoptosis by inhibiting ERK and Mcl-1 which not only induce apoptosis in cancer cells but also in healthy cells. This side effect of the traditional radio and chemotherapies is not exist for SMI since they induce apoptosis via the protein-protein interactions instead of inhibiting Erk or Mcl-1.

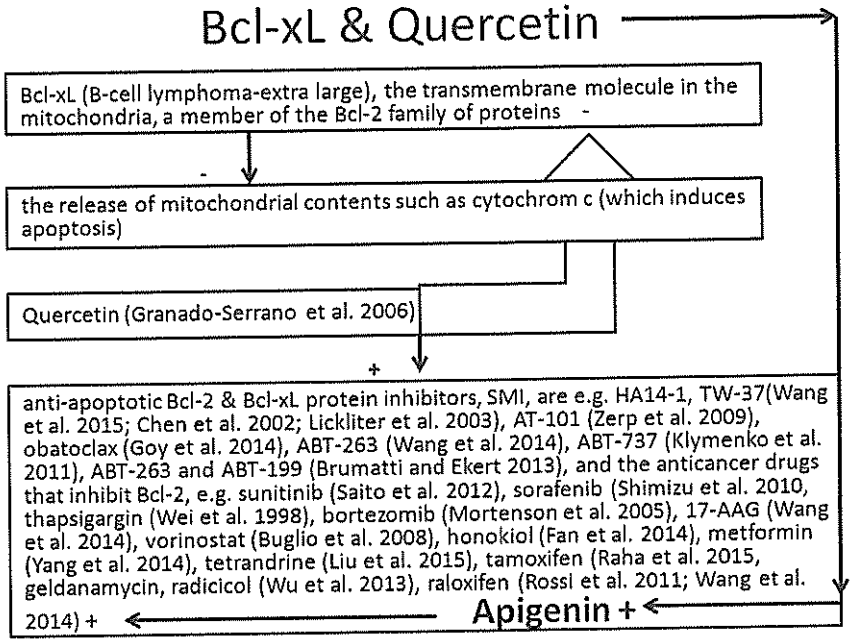


FIGURE 31

Another important anticancer effect of the flavonoid may be due to its inhibitory effect on the signaling of IL-6 and STAT3, the inflammatory cytokine and its activator (Michaud-Levesque et al. 2012; Cao et al. 2014), while the suppression of IL-6/STAT3 signaling by the flavonoid also downregulates the anti-apoptotic Bcl-2 family proteins (Wang et al. 2013). Because of the mentioned inhibitory effect of the flavonoid on IL6 and STAT3; the STAT3 inhibitors; S3I-201, static, STA-21, WP1066, cucurbitacin B, 5,15-diphenylporphrin (5,15-DPP), niclosamide, auranofin, galiellalactone, kahweol, cepharanthine, SD1008, nifuroxazide, cryptotanshinone, ruxolitinib phosphate, STAT 3 inhibitor VII, sunitinib, sorafenib, bortezomib, guggulsterone, paclitaxel, honokiol, metformin, 17-AAG, vorinostat, romidepsin and tetrandrine and IL-6 inhibitors; ; tocilizumab, sunitinib, sorafenib, metformin, radicicol, 17-AAg, monensin, brefeldin A, raloxifene, bortezomib, siltuximab, honokiol, curcumin, may have stronger anticancer effect

if quercetin rich foods are included into the anticancer diet during the treatments with the mentioned anticancer drugs and agents.

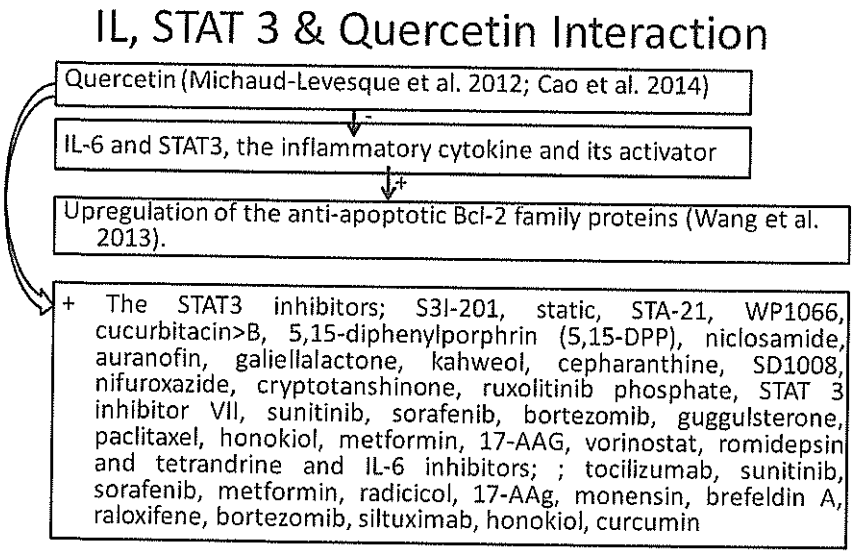


FIGURE 32

Finally, the flavonoid significantly blocks ERK signaling while blocking the signal of ERK, the intracellular anti-apoptotic protein, serine/threonine kinases (Pan et al. 2015). Accordingly, vorinostat, ritonavir, radicicol, tamoxifen, geldanamycin, lapatinib, fulvestrant, PD98059, UO126, honokiol and SNX212 may benefit from the flavonoid rich foods; caper, onion, cocoa, berries, tea, lettuce, asparagus, red leaf and green pepper, creating a synergy to inhibit ERK signaling, opposite to the sulphoraphane rich foods; Brussels sprouts, radish mustard, broccoli, red cabbage, cauliflower, Chinese kale and turnip, all of which activates the signaling and thus may be contraindicated.

The STUDIES about the ASSOCIATION of QUERCETIN with VARIOUS TYPES of CANCER

- 183.518 men and women/529 pancreas cancer/1993-2002/45-75 years of age/smoking adjusted, alcohol adjusted/ 11.77 mg/d (as the highest quartile) (0.80, 0.60-1.06, 95% CI) versus 8.90 mg/d (the lowest quartile) (R:1.00, 95 % CI) decreased the risk(Nöthlings et al. 2007).
- 62440 men and women/1966-1972/39.3±15.8 years of median age/smoking adjusted, alcohol not/3.6 mg/d as the highest quartile of quercetin intake (0.88, 0.78-1.00, 95% CI) versus 2.7 mg/d as the lowest quartile (R:1.00, 95% CI) decreased the risk (Knekt et al. 2002).
- 27111 men/228 renal cancer/50-69 years of age/1985-2002/ alcohol adusted, smoking adjusted/>9.1 mg/d (as the highest quartile)(0.7, 0.5-1.0, 95% CI) versus ≤4.8 mg/d (R:1.00, 95% CI) decreased the risk in male smokers(Wilson et al. 2009).
- 66.940 women/347 ovarian cancer/1984-2002/30-55 years of age/ smoking adjusted and alcohol adjusted/30.7 mg/d (as the highest quartile (0.80, 0.55-1.16, 95% CI) versus 6.3 mg/d (as the lowest quartile) (R: 1.00, 95% CI) decreased the risk (Gates et al. 2007).
- 27111 male/306 pancreatic cancer/50-69 years of age/smoking adjusted, alcohol adjusted/1985-2004/>9.87 mg/d(as the highest quartile)(1.07, 0.75-1.53, 95% CI) versus ≤4.44 mg/d (as the lowest) (R: 1.00, 95% CI) decreased the risk(Bobe et al. 2008).
- 38.408 women/3234 breast, colorectal, lung, endometrial and ovarian cancers/11.5 years of follow up /≥45 years of age/alcohol adjusted, smoking adjusted/ 32.79 mg/d (as the highest quartile) (0.91, 0.81-1.01, 95% CI) versus 6.49 mg/d (as the lowest) (R: 1.00, 95% CI) did not make any effect(Wang et al. 2009).
- 90630 women/710 breast cancer/8 years of follow up/ smoking adjusted, alcohol adjusted/26-46 years of age/30.1 mg/d (as the

highest quartile)(1.05, 0.85-1.33, 95% CI) versus 5.3 mg/d (as the lowest) (R: 1.00, 95% CI) did not make any effect (Adebamovo et al. 2005).

- 71.976 women and 35425 men/878 colorectal cancer/30-55 years of age/1990-1998/smoking adjusted, alcohol adjusted/the highest quartile of total daily quercetin intake (0.75, 1.35-0.40, 95% CI) versus the lowest (R:1.00, 95% CI) did not make any effect (but the amounts of the 5 levels of quartiles are not written in the study!)(Lin et al. 2006).
- 2120 control/2100 lung cancer/2002-2005/64.8-66.3 years of median age/smoking adjusted, alcohol adjusted/the highest quartile of daily quercetin intake(0.46, 0.34-0.64, 95% CI) versus the lowest (R: 1.00, 95% CI) decreased the risk (but the amounts are not written in the published paper!!)(Lam et al. 2010).
- 27110 male smokers/791 lung, 226 prostate, 156 urothelial, 133 colorectal, 111 stomach, 92 renal cancer/50-69 years of age/6.1 years of follow up/alcohol adjusted, smoking adjusted/ the highest quartile (16.3 mg/d)(0.43,0.30-0.61, 95% CI) versus the lowest (4.2 mg/d)(R:1.00, 95% CI) decreased the risk of lung cancer but not others (but the stud does not target only quercetin, instead, the effect of the total flavonols and flavones. Thus, the protective effect against lung cancer can not be attributed to only quercetin!!)(Hirvonen et al. 2001).

RESVERATROL

Resveratrol (trans-3,5,4-trihydroxystilbene) is a phytoalexin, an antimicrobial and an antioxidant substance, synthesized by plants that accumulate rapidly at the areas of pathogen infection, radiation or mechanical injury (Carter et al. 2014). Peanuts and grapes are the richest sources with 1920 and 3540 ng/g, respectively, followed by blueberries with 32 ng/g and red wine with 0.1-14.3 mg/L (Lyons et al. 2003; Vitrac et al. 2005). One of the most important factors which may affect the anticancer potential of resveratrol is the 'pH level' of a given resveratrol rich food or the diet which contains resveratrol. Acidic pH promotes the growth inhibition, apoptosis and DNA damaging capacity of chemopreventive agent resveratrol with an induced internucleosomal DNA fragmentation (Shamim et al. 2012). Thus, the low pH foods, such as; carbonated beverage (2.5 pH), lemonade (3.3 pH), strawberry juice (3.6 pH), white wine (2.9 pH), red wine (3.5 pH), ketchup (3 pH), apple juice (3.1 pH), (3.0 pH), coffee (3.8 pH) and tea (3.9 pH) (Agrawal et al. 2005) may be advised as combined with resveratrol rich foods such as peanuts, grapes, strawberries and blueberries to enhance the growth inhibition and apoptotic effect of resveratrol as long as the patient with cancer is free of reflux. That cancer cells thrive in acidic (low pH), but cannot survive in alkaline (high pH) conditions suggested by unsubstantiated theory is only correct for the cells in an isolated laboratory setting since altering the cell environment of the human body to create less acidic and less-cancer friendly environment is virtually impossible. But opposite, high acidity may be very crucial and beneficial in cancer nutrition since it enhances the apoptotic effect of the polyphenol.

Resveratrol & Cancer

- Resveratrol (trans-3,5,4-trihydroxystilbene), a phytoalexin, an antimicrobial and an antioxidant substance(Carter et al. 2014)
- Acidity increases the anticancer potential of the bio-active compound!
- Acidic pH promotes the growth inhibition, apoptosis and DNA damaging capacity of resveratrol with an induced internucleosomal DNA fragmentation (Shamim et al. 2012).
- A carbonated beverage may not always be harmful when cancer is concerned, provided that it is mixed with a bluuberry or grape juice !

FIGURE 33

One of the anticancer effects of resveratrol appears due to the formation of reactive oxygen species (ROS) induced by the polyphenol by an increase in cleavage of caspase-8 and caspase-3, the cystein-dependent aspartate-directed proteases or cysteine-aspartic proteases, in HT-29 and COLO 201 human colon, human U937 leukemic monocyte lymphoma cells, NSCLC (lung cancer), C7H2 (lymphoblastic leukemia), HCT (human colon carcinoma) and SGC790 (human gastric) cancer cells, which play essential roles in apoptosis (Miki et al. 2012; Juan et al. 2008; Azmi et al. 2006; Guha et al. 2011; Luo et al. 2013; Tinhofer et al. 2001; Heiss et al. 2007; Wang et al. 2012 and Choi et al. 2009).

Caspase-9, one of the members that are the aspartic acid specific proteases belong to the family, distrupts mitochondrial diffusion limit of the apoptogenic molecules such as cytochrome c and serves to amplify further release of cytochrome c to the cytosol (Kim and Park 2003). Caspase-9 is also the initiator caspase which is required for apoptosis signaling through the mitochondrial pathway which is the center of the mentioned cytochrome c release (Würstle et al. 2012). Resveratrol shows a time-dependent loss of mitochondrial membrane potential, in combination with the activation of caspase-9 (Zhang et al. 2011; Dörrie et al. 2001; Lin et al. 2012; Li et al. 2006).

Although the polyphenol is an antioxidant, paradoxically, one of its anticancer effects is formed due to the ROS increase by the antioxidant while cancer cells have already a tendency to produce great amounts of ROS (Zunino et al. 2006; Pelicano et al. 2004; Wang et al. 2008; Sullivan et al. 2014; Liou and Storz 2010; Schumacker 2006; Nogueira and Hay 2013; Barrera 2012 and et al. 2009). The initial reason for the oxidant effect of the antioxidant is that it may upregulate the expression of Nox5, the member of NADPH oxidase enzymes which share the capacity to transport electrons across the plasma membrane and to generate superoxide and other downstream reactive oxygen species (Luo et al. 2013; Bedard and Krause 2007). Another reason for the increase in ROS concentration in spite of the antioxidant polyphenol may be the damage of mitochondrial function as a result of the accumulation of intracellular Calcein AM and the depolarization of the mitochondrial membrane by resveratrol (Sun et al. 2008; Zunino and Storms 2006). Briefly, the natural ROS production capability of the antioxidant, the overexpression of Nox5, the accumulation of intracellular Calcein AM, the depolarization of the mitochondrial membrane and the tendency of cancer cells to produce extremely high amounts of ROS may be the initial reasons for the increases in ROS by resveratrol. Accordingly, the effects of the anticancer drugs which kill cancer cells by producing ROS or whose anticancer effects are induced by ROS, namely; Sunitinib (Rainer et al. 2012; Huang et al. 2011; Nowak-Sliwinska et al. 2015), sorafenib, tetrandrine (Coriat et al. 2012; Wan et al. 2013; Xiao et al. 2015; Liu et al. 2011; Gong et al. 2012; Wang et al. 2015; Choi et al. 2013), cisplatin, paclitaxel (van den Berg et al. 2006; Bragado et al. 2007; Berndtsson et al. 2007; He et al. 2012; Marullo et al. 2013; Gang et al. 2014), bortezomib (Hui et al. 2013; Selimovic et al. 2013), vorinostat (SAHA, subercynalidehydroamic acid) (Ohshima-Hosoyama et al. 2011; Pei et al. 2003), MG-132 (Han and Park 2010; Chen et al. 2014; Park and Kim 2012; Chen et al. 2008), metformin (Queiroz et al. 2014; Haes et al. 2014; Anedda et al. 2008; Gong et al. 2014; Yan et al. 2013 and Liu et al. 2014), thapsigargin, tunicamycin (Lee et al. 2007; McCullough et al. 2015; Lenin et al. 2012; Dolai et al. 2011; Yung et al. 2007), 17-AAG (Sarangi et al. 2012; Mitchell et al. 2007; Fukuyo et al. 2008; Shirazi and Kontoyiannis et al. 2014), DBeQ (Fang et al. 2015; Guillen et al.

2000; Gomez-Toribio et al. 2015), ritonavir (Tarryn-Lee 2014; Wang et al. 2007), leptomycin B (Cromie and Gao 2015), ritonavir (Capel et al. 2012; Reyskens et al. 2013; Wang et al. 2009), brefeldin A (Davies et al. 2006), may be enhanced by resveratrol and resveratrol rich food consumption during the treatments with the mentioned drugs since one of the anticancer effects of the antioxidant is via the increase in ROS and targeting tumor cells with ROS when the antioxidant is used as 50-200 μmol/L/48h (Miki et al. 2012; Luo et al. 2013; Heiss et al. 2007; Hussain et al. 2011; Juan et l. 2008; Wang et al. 2012).

Estrogens, which have long been recognized as being important for stimulating the growth of a large proportion of breast cancers, are in close interaction with resveratrol. One of the two receptors that mediate the action of estrogen, estrogen receptor alpha (ERalpha) correlates with better prognosis and the likelihood of response to hormonal therapy since over half of all breast cancers overexpress ERalpha while around 70 % of them respond to anti-estrogen therapy (Ali and Coombes 2000). The other estrogen receptor (ERbeta) suppresses the function of ERalpha as in cooperation with ERbeta and may lead to a better prognosis (Weihua et al. 2000; Hayashi et al. 2003). Resveratrol differs from other phytoestrogens which which bind ERbeta with higher affinity than ERalpha since, as in contrast, resveratrol shows no estrogen antagonist activity with ERbeta (Bowers et al. 2013). The anticancer effect of the drugs and hormones which are the ERalpha antagonists in some cancer treatments especially breast cancer, namely; tamoxifen, raloxifene, fulvestrant (ICI) (Sun et al. 2002; Barkhem et al. 1998; Jaber et al. 2006; Long and Nephew 2006; Yeh et al. 2013; Leblanch et al. 2007; Jisa et al. 2001; Bryant et al. 1999; Dayan et al. 2006; Gruvberger-Saal et al. 2007; Mc Ilroy et al. 2006), C1618 (Young et al. 2001), nafoxidine, hexestrol, dienestrol (Kuiper et al. 1997; Paech et al. 1997) can be enhanced by the consumption of resveratrol rich foods or resveratrol supplements during some of the hormone related cancer treatments since both drugs and resveratrol/resveratol rich foods are ERalpha antagonists and hence, may form a synergy, yielding a much stronger anticancer potential via the increase in ERbeta levels, in case of their combined uses.

The androgen receptor (AR), also known as NR 3C4 (nuclear receptor subfamily 3, group C, member 4) is a nuclear receptor that is

activated by binding either of the androgenic hormones, testosterone or dihydrotestosterone (Lu et al. 2006; Roy et al. 1999). The main function of the androgen receptor is, as a DNA-binding transcription factor, a protein that binds to specific DNA sequences and thus controlling the rate of transcription of genetic formation from DNA to messenger RNA (Latchman 1997 and Karin 1990), to regulate the gene expression (Mooradian et al. 1987).

Some hormone related cancers, especially prostate cancer, are often associated with the alterations in androgen receptors. The drugs that prevent the production of androgen and/or block the action of the androgen receptors inhibit prostate cancer growth (Eileen Tan et al. 2015; Suzuki et al. 2003). Confirming this, enzalutamide, an androgen receptor (AR) inhibitor which blocks estrogen receptor(ER) inhibits estradiol (E2)-mediated proliferation of breast cancer cells as a result of its block on ER (Cochrane et al. 2014). The most important detail here is that the most identified androgen receptor mutations from hormone refractory prostate cancer are capable of transcriptional activity and also androgen receptor is expressed throughout prostate cancer progression and persists in the majority of patients with hormone refractory disease, indicating that loss of androgen receptor function is not a major cause of androgen ablation (AR) failure) and AR-negative prostate cancer cells do not have a significant growth or survival advantage (Mohler et al. 1996; Hobisch et al. 1996 and Heinlein and Chang 2004). Resveratrol inhibits the expression of ARA70 (Mitchell et al. 1999) that this inhibition may be another reason for the decrease in the risk of prostate cancer by the means of resveratrol rich foods or supplementation.

The signaling axis of the androgen receptor plays a critical role in the development, function and homeostasis of the prostate. On the other hand, prostate cancer initiation and progression is uniquely depended on androgen receptor and its signaling axis. Although the deprivation therapy using the namely mentioned androgen receptor antagonists mentioned above remains the standard care for treatment of the cancer with a favourable response, in almost all patients invariably progress to a more aggressive, castrate-resistant phenotype of the cancer (Lonergan and Tindall 2011). Any mutation besides the signaling axis or any abnormal signaling of AR due to the mutation may cause prostate cancer.

Resveratrol represses the transcriptional activities of a mutant AR, lacking the ligand-binding domain, a wild-type AR in a concentration-dependent manner in human prostate cancer PC-3 cells. The flavonoid down-regulates AR protein through a post-translational mechanism while decreasing the post-translational AR level and repressing AR transcriptional activity (Harada et al. 2007; Shi et al. 2009). Briefly, agents targeting the androgen receptor axis, the initial chemoprevention and treatment of prostate cancer at all states of the disease, may show a much greater anti-cancer effect if combined with resveratrol and resveratrol rich foods since both androgen receptor antagonists and resveratrol target the androgen receptor axis, down-regulate AR protein and decrease the post-translational AR level. Confirming this, the combination of resveratrol (1-100μM) with the androgen receptor antagonist, flutamide (10^{-4}M), has the mentioned synergistic effect on the down-regulation of AR, reducing the amount and activity of AR, suggesting new therapeutic strategies, in prostate cancer treatments, which are confirmed in the prostate cancer cell lines; LNCaP, PC3 and Dul45 (Kai and Levenson 2011).

One of the repressions of AR by resveratrol in LNCaP prostate cancer cells occur on androgen up-regulated genes; the anterior gradient 2(AGR2) and anterior gradient 3(AGR3) comprising two highly related genes encoding secretory proteins that are expressed in prostate cancer while the former has been associated with tumor metastasis (Bu et al. 2013), c-MYC, c-MYC purine-binding transcription factor (PuF), macrophage migration inhibitory factor (MIF), macrophage inhibitory cytokine-1 (MIC-1), lactate dehydrogenase-A (LDH-A), guanine nucleotide-binding protein Gi, α-1 subunit (NBP), cyclin dependent kinase-2 (CDK-2), prostate-specific membrane antigen (PSM), cyclin H (CCNH), 60S ribosomal protein L10 (RPL10), 60S ribosomal protein L32(RPL32) and 40S ribosomal protein S16(RPS16), the genes all of which are correlated with the progression of human prostate cancer (Karan et al. 2002). Another inhibitory effect of the polyphenol on AR is via to human glandular kallikrein-2, a prostate specific kallikrein (serine protease), produced by prostatic epithelium which is a prostate cancer tumor marker (Rittenhouse et al. 1998; Seeni et al. 2008; Wang et al. 2008). E2F3, a protein, encoded by E2F3 gene, plays a crucial role

in control of cell cycle and action of tumor suppressor proteins. But, the overexpression of the protein leads to the development of malignant bladder, lung and prostate cancer (Foster et al. 2004; Vimola et al. 2012; Feber et al. 2004; Pipinikas et al. 2007). Cell cycle points are the control mechanisms in eukaryotic cells which ensure proper division of the cell. Each check point serves as a halting point during cell proliferation which the conditions of the cell to proliferate are assessed with progression through the various phases of the cell cycle occuring when favourable conditions are met. The three currently known checkpoint are; the G1/S checkpoint, the G2/M checkpoint and the metaphase check point (the second period of mitotic division). At this point, the main mechanism in the carcinogenic effect of the gene is that the E2F3 expression correlates with the removal of retinoblastoma protein (pRB) suppressor control at the G1/S transition in the cell cycle (Foster et al. 2004). Thus, the overexpression of the gene removes the suppression and halting on cell proliferation, leading to cancer. Unfortunately, in spite of many anticancerogenic effects, when the gene is considered, resveratrol has been found to upregulate the gene, E2F3, and thus, it may limit the anticancerogen effects of the drugs, namely; vinblastine, oncovin, navelbine, taxol, taxofere, atropine, flavopiridol, berberine, lomustine, mitolactol, cisplatin, fenretinide, fenretinide 4-hydroxy, phenyl retinamide, idarubicin, nafoxidine, megestrol acetate, megastrol, testolactone and fadrozole (Skariyachan et al. 2010), the drugs that bind the gene and therefore may be contraindicated with resveratrol supplementation or resveratrol rich foods.

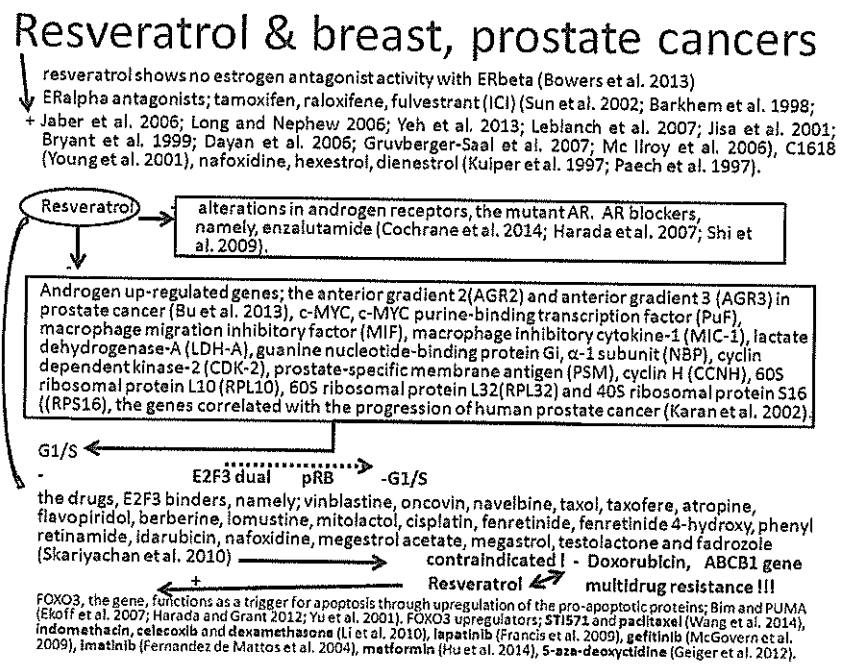


FIGURE 34

FOXO3, the gene which is a transcription factor, functions as a trigger for apoptosis through upregulation of genes which are necessary for cell death, the pro-apoptotic proteins such as Bim and PUMA (the p53 upregulated modulator of apoptosis) (Ekoff et al. 2007; Harada and Grant 2012; Yu et al. 2001). On the other hand, the over-expression of phosphorylation deficient FOXO proteins which induce FOXO transcriptional activity is further enhanced by resveratrol (Chen et al. 2010; Lin et al. 2014; Mukherjee et al. 2009). The anticancer effects of the drugs which inhibit cell proliferation by upregulating FOXO3; STI571 and paclitaxel (Wang et al. 2014), indomethacin, celecoxib and dexamethasone (Li et al. 2010), lapatinib (Francis et al. 2009), gefitinib (McGovern et al. 2009), imatinib (Fernandez de Mattos et al. 2004), metformin (Hu et al. 2014), 5-aza-deoxyctidine (Geiger et al. 2012), may benefit from resveratrol supplementation or resveratrol rich food consumption, forming a synergy for a stronger apoptosis via the upregulation FOXO3. But, resveratrol supplementation or resveratrol

rich foods should be avoided during the treatment with doxorubicin because doxorubicin induces the expression of multidrug resistance gene ABCB1 (MDR1) after activating FOXO3 (Hui et al. 2008).

That AGR2 is a direct target of endoplasmic reticulum (ER) is the initial reason for the cancerogenic effect of the gene. Thus, the decreased AGR2 levels may be the new promising target of estrogen therapy (Salmans et al. 2013). But, tamoxifen blocks the binding of estradiol to its receptor while inducing ER binding to AGR2 which results in increase of AGR2 levels (Hrstka et al. 2010). On the other hand, resveratrol is a phytoestrogen with low ER affinity that the induction of many estrogen-sensitive genes is not increased by the polyphenol or the other phytoestrogens like coumestrol or enterolactone. But, it is surprising that these weak phytoestrogens with low ER affinity interact with other estrogenic antagonists, like the interaction between 'resveratrol and enterolactone', 'resveratrol and coumestrol' or 'resveratrol, enterolactone and coumestrol'. Confirming this, the combined use of the equal concentrations of these pohytoestrogens increase the expression of cancer genes including AGR2 more than their alone administrations (Dip et al. 2009).Thus, coumestrol rich foods; legumes, clover, chick pea, alfalfa, spinach, Brussels sprouts, soybeans (Bhagwat et al. 2008), resveratrol rich foods; garpes, blueberries, raspberries, mulberries (Jasinska et al. 2013) and red wine (Azorin-Ortuno et al. 2012) and enterolactone rich foods; flaxseed and sesame seed, should be avoided during the cancer treatment with tamoxifen since such nutrition or supplementations can decrease the anticancer effect of the drug since they also increase the expression level of the cancerogenic gene, AGR2, like tamoxifen. The same advice to avoid from the combined supplementation or consumption of resveratrol, enterolactone and coumestrol rich foods may also be useful during the treatments with tunicamycin, bortezomib and 4-hydroxytamoxifen (40HT), since these drugs inhibit the expression of the carcinogenic gene, AGR2, while the combined or alone supplementations or consumptions of resveratrol, enterolactone and coumestrol, may increase the expression of the gene and thus, may be contraindicated with the mentioned drugs.

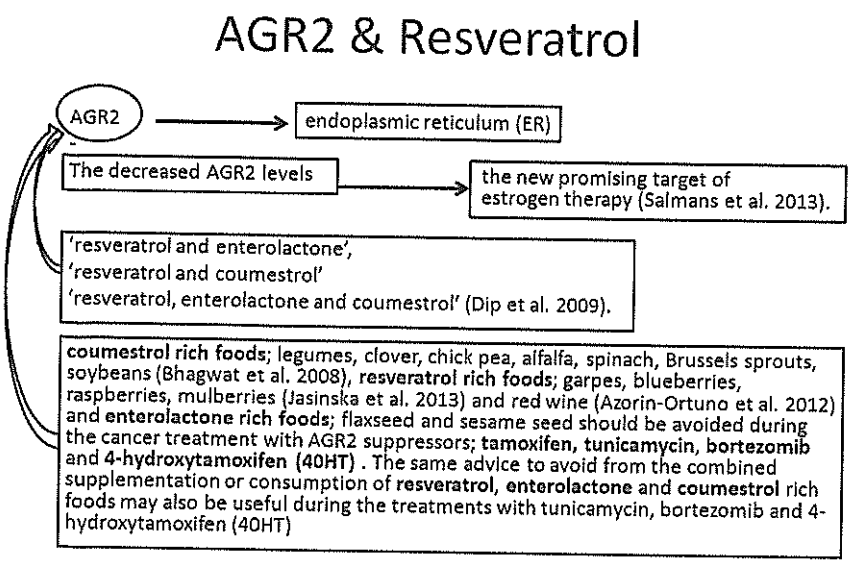


FIGURE 35

Sphingosine-1-phosphate (S1P) is a sphingolipid (a class of lipids containing a backbone of sphingolipid base, a set of aliphatic aminoalcohols) which promotes cell survival and proliferation, inducing cell growth and apoptosis. Sphingosine kinase (SphK1) catalyzes the phosphorylation of sphingosine to S1P and thus, the enzyme has emerged as a new target in cancer treatments to ihibit cell proliferation (Shida et al. 2008). The drugs which show anticancer effect by inhibiting SphK1SKI-5C (Datta et al. 2014), 5-fluorouracil (5-FU) (Tan et al. 2014), etoposide, melphalan, cisplatin, carboplastin, topotecan, paclitaxel, vincristine, safingol (Kim et al. 2006), 2-alkyl-2-amino-1,3-propanediol (FTY720) (Kharel et al. 2005, 2-(p-hydrocxyanilino)-4-(p-chlorophenyl)thiazole, sphingomab (Takabe et al. 2008), (2R, 3S, 4E)-N-methyl-5-(4'-pentylphenyl)-2-aminopent-4-ene-1,3-diol (Paugh et al. 2008), may show greater anticancerogenic effect if they are administered as combined with resveratrol supplementation or resveratrol rich foods, since resveratrol, like the mentioned drugs, inhibits sphK1 (Abdin 2013; Brizuela et al. 2010).

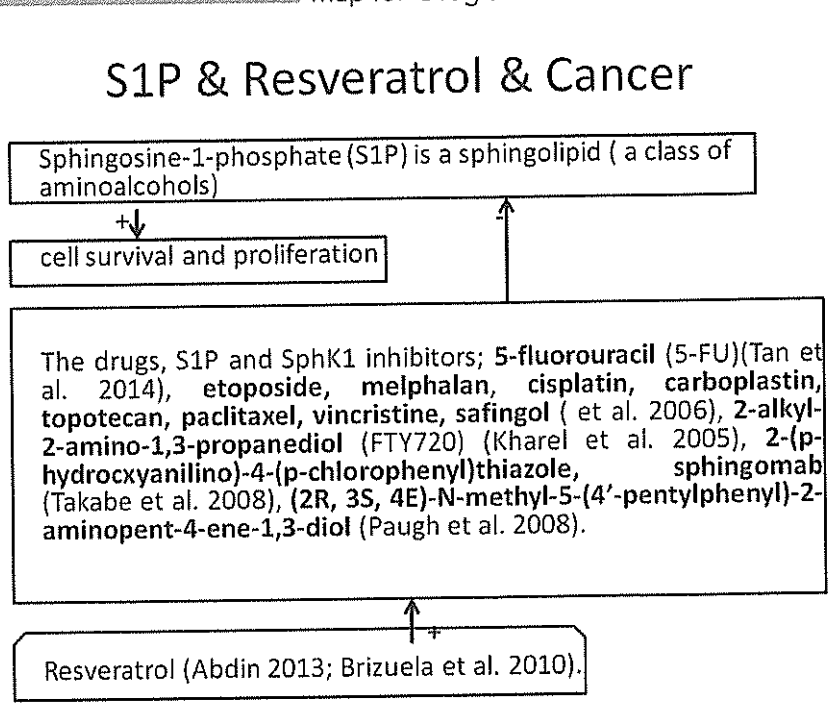


FIGURE 36

The Hedgehog signaling is a signaling pathway that transmits information with Hedgehog proteins to embryonic cells. The information transmitted by Hedgehog is required for the proper development of the cell and the signaling is often considered as one of the reasons for cancer (Jiang and Hui 2008). The signaling pathway begins with binding of Hedgehog (Hh) to Patched (Ptch1), a 12-transmembrane morphogen receptor which inhibits the activity of another transmembrane protein, Smoothened (Smo). The binding of Hhto Ptch1 relieves the inhibition of Ptch on Smo (Evangelista et al. 2006), leading to the activation of Smo which can act as an oncogene, a gene that has the potential to cause cancer. Thus, the overactivation or overexpression of Hh acts as a Smo activator which results in cancer. The relation with the overactivity and expression of Hh signaling and cancer is well documented in small cell lung cancer, pancreatic cancer, prostate cancer, medulloblastomas and basal cell carcinomas (Wang et al. 2013; Atwood et al. 2012; Hahn et al. 1996; Xie et al. 1997; Hettmer et al. 2013) due to the mutations

that activate the Hedgehog signaling pathway. The anticancer effects of the drugs which act by inhibiting Hh signaling pathway, currently administered; the synthetic cyclopaminela plant alkaloid in corn lily, CUR-61414, HhAntag-691, GDC-0449 (in basal cell carcinoma, medulloblastoma and rhabdomyosarcoma) (Rudin et al. 2009; Scales and de Sauvage 2009; Von Hoff et al. 2009; Kolterud and Toftgard 2007; Taipale et al. 2000), guggulsterone (a plant steroid, obtained from Commiphora mukul (Dixit et al. 2013), soridegib(IPI-926) (in advanced solid tumors) (Jimeno et al. 2013), phthaladines, namely LY2940680, NVP-LEQ506 (Karhadkar et al. 2004; Watkins et al. 2004), itraconazole, an antifungul (in meddulloblastoma) (et al. 2010), NVP-LDE225 (Epstein 2008), TAK-441 (Kogame et al. 2013), XL-139 (Tremblay et al. 2009), HTS piperidines (Yuan et al. 2007; Berman 2003), MRT-83 (Roudant et al. 2011), PF-04449913 (acute myeloid leukemia (Fukushima et al. 2013), N-acylethanolamides, 2-acylglycerols and 2-alkylglycerol (endocannabinoids) (Khaliullina et al. 2015) may increase if the mentioned frugs are administered as combined with resveratrol supplementation or resveratrol rich food consumption since resveratrol, like the drugs, has an antagonizing effect on the hedgehog signaling pathway protein members including Gli1, Ptc1 and Smo CCND1, Bcl-2 (Bai et al. 2014, Mo et al. 2011; Gao et al. 2015).

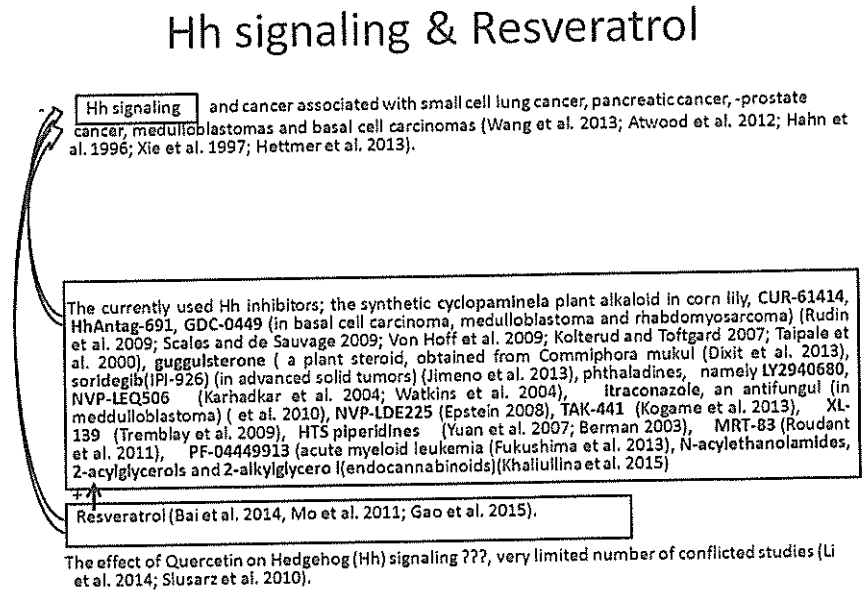


FIGURE 37

Not only resveratrol and resveratrol rich foods like grapes, blueberries, raspberries, mulberries (Jasinski et al. 2013) and red wine (Stervbo et al. 2007), but also Genistein and genistein rich foods like; currants, raisins, satsumas, Brazil nut, chestnut, coconut, bazelnut and sesame seeds (Liggins et al. 2000), curcumin and curcumin rich foods; turmeric and ginger (Mishra and Palanivelu 2008), EGCG (Epigallocatechin gallate) rich foods; white tea, green tea and black tea, dark chocolate, fava beans, pears, raspberries, cherries, blackberries, apples (Lorenz and Urban 2009; Heneman and Zidenberg-Cherr 2008), apigenin and apigenin rich foods like; parsley and celery (Manach et al. 2004), baicalein rich foods like; *Scutellaria baicalensis* (or Huang Qin, also known as the Chinese skullcap), carrot, celery and broccoli (Birt et al. 2001; Huang et al. 2010), quercetin and quercetin rich foods like onions, kale, broccoli, lettuce, tomatoes, asparagus, red leaf, lettuce and green pepper (Lam et al. 2012; Nishimuro et al. 2015; Slusarz et al. 3382) inhibit the Hedgehog signaling pathway and thus, the combined nutrition of the foods rich in the mentioned flavonoids may strongly be advisable during the treatments by the anticancer drugs mentioned

above. But, it should be noted that, alcohol consumption is one of the leading causes of cancer (Bagnardi et al. 2001; Fowke et al. 2014; Li et al. 2014 and Conroy et al. 2012), since it alcohol is the antagonist of all the mentioned drugs and nutrients which are Hedgehog antagonist.

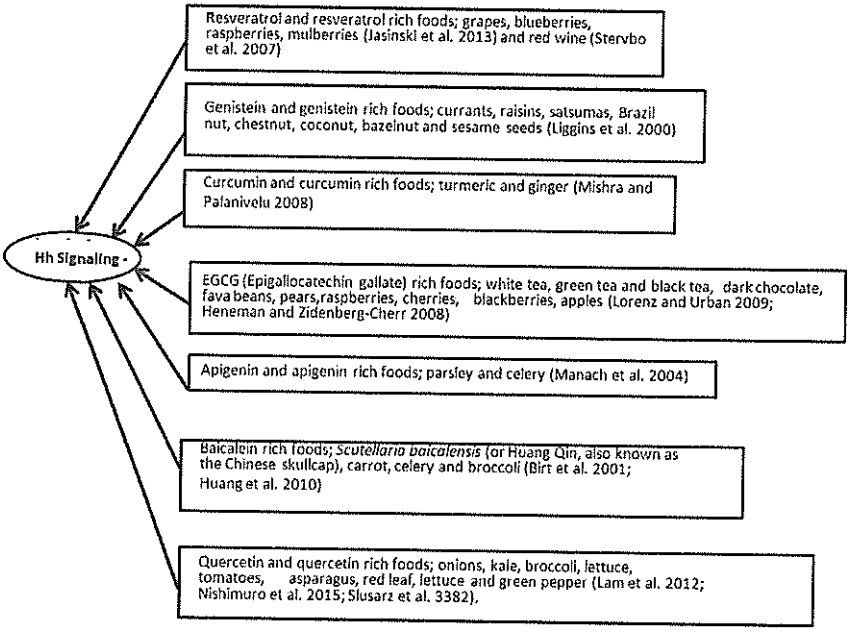


FIGURE 38

Insulin-like growth factor (IGF-1), also called somatomedin C, is a protein which is similar in molecular structure to insulin. The hormone plays an important role in childhood growth and it has anabolic effect in adults. IGF-1 binds to insulin receptors with a low affinity and thus, the hormone has been postulated to be a mediator of enhanced insulin action (Moses et al. 1996). On the other hand, growth hormone (GH) which is secreted from the anterior pituitary synergizes with IGF-1 (Doughaday 1989). As in the synergy with GH, IGF-1 exerts powerful effects on cancer development and cellular proliferation, angiogenesis, metastasis and resistivity development to chemotherapeutic agents (Laban et al. 2002; Bustin and Jenkins 2001). IGF-1 is a hormone which acts as a powerful antiapoptotic agent, influencing the apoptotic responses to a

variety of agents of numerous cell types. The antiapoptotic actions of the hormone tend to be mediated via the PI-3 kinases (phosphotidylinositol 3 kinase), the enzymes which are involved in cell growth, proliferation, differentiation, motility, survival and cancer (Molina,Arcas et al. 2013; Paek et al. 2010; Chalhoub et al. 2009; Sheppard et al. 2012). IGF-1 (10 nM) elevates glucose-6-phosphate dehydrogenase whose overexpression leads to cell proliferation (Kuo and Tang 1999). The induction of the enzyme, glucose-6-phosphate dehydrogenase, has been informed to be exist in liver tumors in rats, estrogen-induced kidney tumors in hamsters and also breast, endometrial, cervical, prostate and lung cancers in human (Simile et al. 1995; Roy and Liehr 1988; Bakun et al. 1987; Furuta et al. 2010; Ding et al. 2015; Hu et al. 2013 and Dessi et al. 1988). The following drugs; DHEA (dehydroepiandrosterone), 6-AN(6-aminonicotinamide) (Polimeni et al. 2011), the novel derivatives of the steroid DHEA1 which are produced by androstane nucleus with a pregnane nucleus and pregnan-20-ones incorporation of 21-hydroxyl group (Hamilton et al. 2012), chloroquine (Safeukui et al. 2004), Flutamide and rasburicase (Frank 2005) inhibit G6PD. Ascorbic acid (vitamin C), like resveratrol and the mentioned drugs inhibit G6PD (Rege et al. 2013). Therefore, following a diet rich in resveratrol, vitamin C and fava bean may enhance the anticancerogenic effect of the mentioned drugs via the inhibition of G6PD. On the other hand, resveratrol increases G6PDH (Vanamala et al. 2011; Rege et al. 2013) and this may be useful since G6PDH is an antioxidant and expressed normaly in healthy subjects without cancer. But, the cancer patients face with the overexpression of the enzyme, triggered by IGF-1 which stimulates cell proliferation. For this reason, resveratrol and resveratrol rich foods like grapes, blueberries, raspberries, mulberries and red wine during the treatments with the mentioned anticancer drugs; DHEA 1, 6-AN, steroid DHEA 1, chloroquine, flutamide and rasburicase may enhance the anti-cancer effect of each other via the inhibition of G6PDH. The other crucial point in cancer nutrition during these drug administrations, vitamin C and vitamin C rich foods like kiwi, guava, papaya, mango, Brussels sprout (Halliwell 2001), citrus fruits and other green leafy vegetables like Brussels sprout (Block 1991) and fava bean which is also another antagonist of G6PDH which produces semiquinoid

divicine radical, superoxide, H_2O_2 and other oxygen products (Arese et al. 2012).

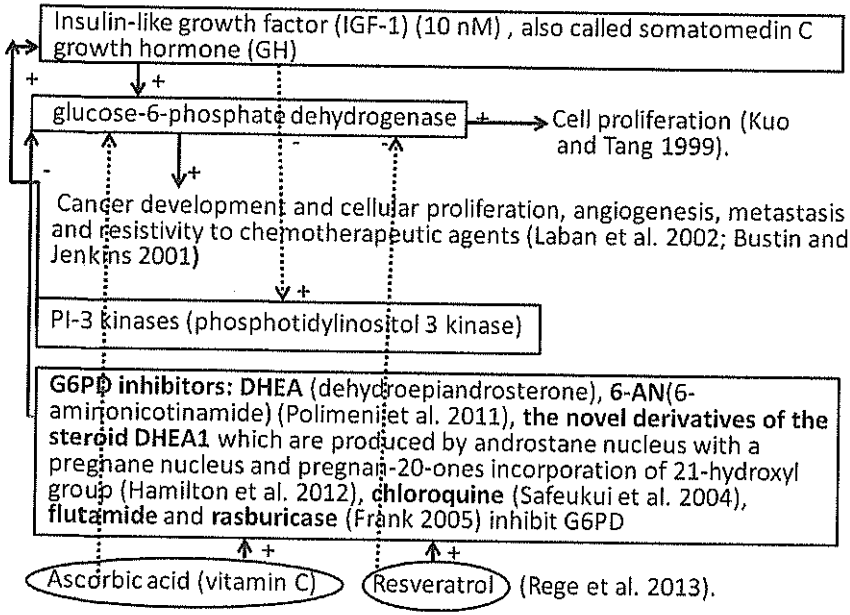


FIGURE 39

Akt, a serine/threonine-specific protein kinase, plays a key role in multiple cellular processes such as glucose metabolism, apoptosis and cell proliferation. But, the signaling from phosphatidylinositide 3-kinase/pAkt (phosphorylated Akt) can lead to radiation resistance during radiotherapy in human cancers (Kim et al. 2006). On the other hand, Akt phosphorylation shows a significant increase in human head and neck tumor tissues (Islam et al. 2014). The overexpression of the enzyme is also exist in advanced pancreatic cancer (Ormanns et al. 2014), non-small cell lung cancer (David et al. 2004), colon cancer (Itoh et al. 2002), breast cancer (Yang et al. 2015), gastric cancer (Jieer et al. 2014), cervical cancer (Korolenkova et al. 2010). Resveratrol inhibits the expression of the enzyme and decrases the enzyme activity, interfering the pAktl/p70S6K signaling, Akt/miR-21 signaling, PI3-K/pAKT pathway but it is crucial to note that the resveratrol amount for the

target should be ≥50 mg/kg BW (Zhang et al. 2013; Sheth et al. 2012; Sexton et al. 2006; Jung et al. 2013; Bhardwaj et al. 2007; Singh et al. 2011). Therefore, the effects of the anticancer drugs which inhibit p-Akt, namely; LY29002, SF-1126 (Garlich et al. 2008), NVP-BEZ235 (Maira et al. 2008), XL147, XL765, ISC-4, GSK690693, MK-2206 (which has strong synergistic effects with the other anticancer agents;erotinib, lapatinib, doxorubincin, camptothecin, gemcitabine, 5-FU, carbolatin and docetaxel) (Chen 2012; ; Yu et al. 2014), fused pyrimidines (Kaur et al. 2014), phosphatidylinositol (3-5) triphosphate (PIP3) (Chang et al. 2014), GDC-0041 (Burrows et al. 011), celecoxib (Hsu et al. 2000), 7-hydroxystarosporine(UCN-01) (Kondapaka et al. 2004), BX-795 BX-912 and BX-320 (Feldman et al. 2005), CCT12830, GDC-0068 (Yap et al. 2011; Blake et al. 2012), perifosine (Gills and Dennis 2009), GSK-2141795, GSK2110183 (Dumble et al. 2014), Ipatasertib (GDC-0068) (Bang et al. 2014), Afuresertib (GSK2110183) (Spencer et al. 2014), AT13148 (Yap et al. 2012), PF-0461502 (Fang et al. 2013), AT867 (Grimshaw et al. 2010) and triciribine (Evangelisti et al. 2011), may be enhanced by resveratrol and resveratrol rich foods during the treatments with the mentioned drugs via the inhibition of pAkt.

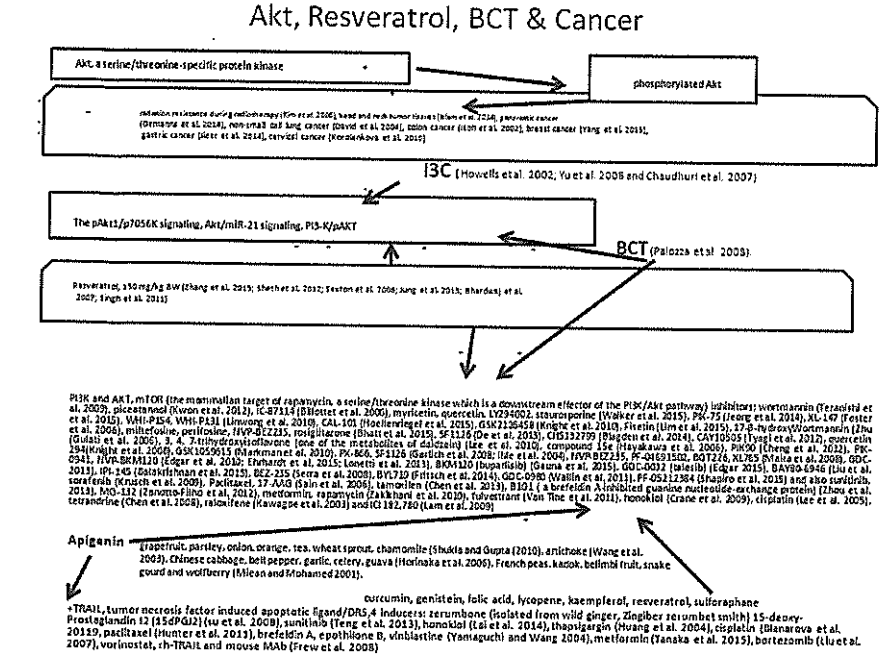


FIGURE 40

Tumor protein p53, the protein which is crucial in multicellular organisms prevents cancer in multicellular organisms and functions as a tumor suppressor (Surget et al. 2013). But, genetic variations due to somatic mutations in the tumor suppressor gene and inactivation by single–base substitution or loss of alleles in the gene and inactivation by viral or cellular proteins play a crucial role in cancer (Hollstein et al. 1991; Tommasino et al. 2003). Resveratrol has been informed to allow p53 acetylation while suppressing the metastasis-associated protein 1 (MTA1), the protein which deacetylates and inactivates p53 (Kai et al. 2010). The crucial point which should be taken into consideration as related to the resveratrol and p53 association is the chemotherapeutic effect of resveratrol by increasing p53 protein levels, even in H1299 (non small cell lung carcinoma) cells that have a partial deletion of the gene (da Costa et al. 2012; Huang et al. 1999; Liontas and Yeger 2004). Resveratrol has also been claimed to trigger apoptosis as independent from p53 in wild-type (mutated) p53-expressed HCT116 carcinoma cells

(Mahyar-Roemer et al. 2001). Moreover, Costa et al. (2014) claims an indication between resveratrol and the wild type p53 while their findings indicate to the ability of resveratrol to inhibit the wild-type p53 core domain as well as the R248Qp53 mutant to undergo in vitro aggregation and reduce the formation of nuclear p53 aggregates. Confirmingly, colon cancer cells with the p53 gene deleted are more sensitive to doxorubicin (Bunz et al. 1999). The activation of p53 includes the use of chemoradiation, gene therapy to introduce wild type p53 or modified adenovirus to kill cancer cells with mutant p53 and synthetic peptides or nongenotoxic small molecules, all of which are the various p53 activators, administered currently (Wang and Sun 2010). Cancer cells with a wild type p53 are more sensitive to chemoradiation (O'Connor et al. 1997; Gudkov and Komarova 2003) while MCF7 breast cancer cells and HCT116 colon cancer cells with p53 either abrogated or deleted are more vulnerable to chemoradiation (Fan et al. 1995; Gupta et al. 1997).

One anticancer treatment using p53 is the activation of wild type p53 by inhibiting its negative regulators like Mdm-2 (Murine Double Minute-2, Hdm2 in human) which binds to p53 and blocks it and acts as an E3 ubiquitin ligase (a protein that recruits an E2 ubiquitin ligase, a protein thar recruits an E2 ubiquitin-conjugating enzyme which catalyzes the ubiquitination (the addition of amino acids to lysine) reaction that targets p53 to degrade it (Freedman et al. 1999 and Xiong 2001). In some of such treatments, nutlins, a class of small molecules which disrupt the binding between Mdm2 and p53, benzodiazepinedione (BDA) which interacts with the p53-binding pocket of Mdm2 and MI-219, MI-63 and MI-43, the spiro-oxindole compounds which mimic Mdm2E3, Mdm2-containing residues (Samudio et al. 2010; Zheng et al. 2010; Shangary et al. 2008), CDB3 (a short synthetic nine-residue peptide, derived from p53-binding protein 2, a known p53-binding protein that interacts with the p53 core domain and upregulates it) (Samuels-Lev et al. 2001), p53 C-terminal peptide (peptide 46, which is derived from p53 C-terminal region) which increases sensitivity in radio-cancer therapy, especially in (wild-type) p53 cancer cells (Ohnishi et al. 2004), CP-31398 (the small molecule with the activity to change p53 conformation from mutant to wild type and stabilize the core domain and enhance transcriptional activity of p53 while upregulating the p53 target genes; p21WAF1/Cip1

and KILLER/DR5) (Takimoto et al. 2002), 37AA (the peptide which consists of 37 amino acids from p53 and induces apoptosis through activation of p53/p73 target genes (Bell et al. 2007), JJ78:12 (another small bioactive molecule which depolymerizes tubulin proteins and activates p53) (Staples et al. 2008), tenovin-6 (the water soluble analog of tenovin-1) which induces apoptosis while activating p53 and inhibiting SIRT1 and SIRT2 (Jin et al. 2015) and tenovin-1 (Lain et al. 2008). The anticancer effects of all the mentioned p53 activators may be enhanced if they are administered as combined with resveratrol or resveratrol rich food consumption.

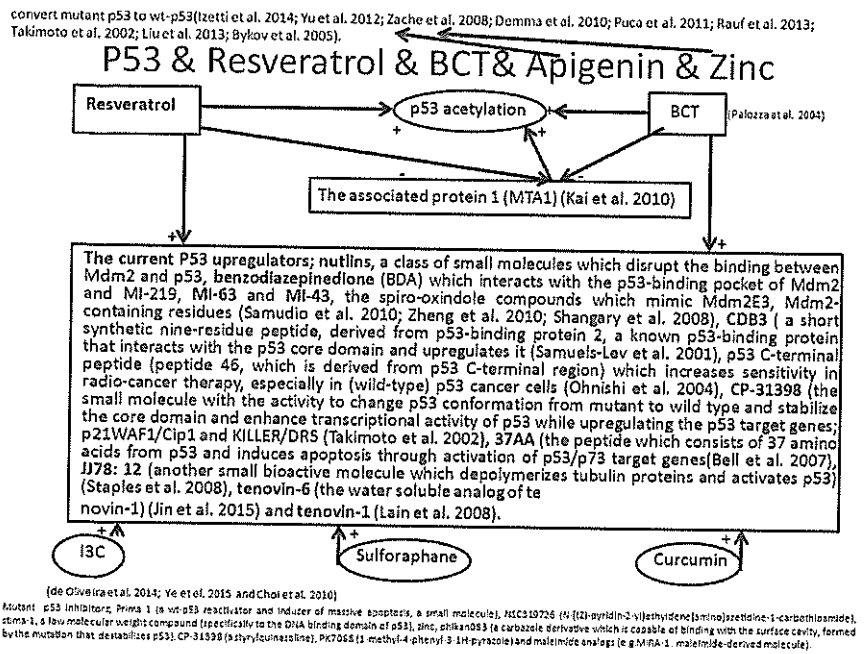


FIGURE 41

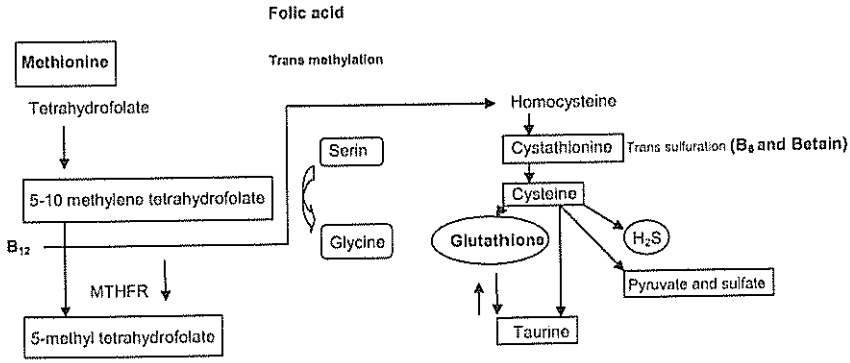
The main paradox and failure about resveratrol cohorts

Many from a limited number of cohorts about resveratrol and its effect on cancer use red wine and other alcoholic beverages as study material since they are the richest sources of resveratrol. For example, Kim et al. (2010) and Semba et al. (2014) did not observe any significant decrease either in epithelial ovarian cancer risk or mortality rate from cancer in wine and never drinkers (1.13, 0.92-1.38, 95% CI) in spite of the rich content of resveratrol in wine, in the meta-analysis of 3 cohort and 7 case control studies, using 135.871 women who are consisted of 65.578 of wine and 70.293 never drinkers. Sutcliffe et al. (2007) inspected a slightly increased the risk of prostate cancer in men who consumed >4 glasses of red wine a week during 1986-2002, with 3348 cases of prostate cancer (as smoking adjusted) in their cohort. Based on these large scale cohorts, any claim that indicate no anticancerogen potential of resveratrol is inevitably becoming far from being in scientific value since it not so difficult to expect that resveratrol may have not exhibited its well-documented anticancerogen effects in alcoholic beverages rich in resveratrol like wine, because of ethanol and its cancerogenic effects causing aldehyde dehydrogenase 2 (ALDH2), mainly due to the activation of p38MAPK (Mutagen Activated Protein Kinase) by ethanol (Brooks et al. 2009, Katsouyanni et al. 1994, Guo et al. 2011, Xu et al. 2015, Winstanley et al. 2011). Chang et al.(2007) observed an increasing effect of one glass of wine daily on the risk of developing ovarian cancer (1.57, 1.11-2.22, 95% CI), compared to no wine in 90.371 subject with ages, 18-35, including 253 women with epithelial ovarian cancer. Confirmingly, Lachenmeir et al. (2014) points out that, for intake of one 100-mL glass of wine, the average margin of exposure (MOE) is 4.1 for ethanol and 459.937 for resveratrol (to understand easier, 4.1 unit of ethanol may be assumed as the equal of 459.937 unit of resveratrol). 111 glasses of wine is needed to be consumed daily to reach Benchmark dose (BMD) of resveratrol to be able to have its therapeutic effect. The MOE ratio between resveratrol and ethanol is

166.128 on average, meaning that per glass of wine, ethanol is more than 100.000 times more potent than resveratrol. Briefly, the number of cohorts about 'resveratrol and cancer' association is very limited, most of which use alcoholic beverages as study material. Cohorts which study 'resveratrol rich, but ethanol free!' foods and drinks are needed to carry out such studies to be able to talk about their scientific credibility and evaluate the anticancerogenic effect of resveratrol alone without a possible associated cancerogenic effect of ethanol!!.

Sulphur

Prevention from cancer by sulphur may be due to its strong ability to manufacture glutathione, **its capacity to neutralize free radicals and reactive oxygen species and** its **function to detoxify poisonous compounds. Sulphur deficiency has been found as a leading factor to glutathione deficiency in some studies (Paterson** et al. 2001; Lyons et al. 2000; Thielemann, 1990; Hunter and Grimble 1997). The use of sulphur in the production of one of the important antioxidant and anticancerogen enzymes, glutathione, has just been detected confirming the theory of sulphur use in glutathione production. Homocysteine, the cancerogen and inflammatory agent, uses methione as sulphur donor and forms cystathionine by using sulphur resulting in a decrease in the concentration of anticancerogen and inflammatory homocytein while cystathionine forms glutathione via to cysteine resulting in an increase of glutathione (Belalcazar et al. 2013). Briefly, sulfur may contribute to cancer prevention with two opposite actions both of which are beneficial; producing the anticancerogen and antioxidant glutathione and decreasing the concentration of inflammatory and cancerogen homocytein



(Bauchart-Thevret et al. 2009)

FIGURE 42

The other anticancerogenic effect of sulphur is due to its increasing effect on glucosinolates. Sulphur supplementation increases the content of total glucosinolates in the cruciferous sprouts, cabbage (*Brassica oleracea*), broccoli (*Brassica capitata*) and radish (*Raphanus sativus*), showing a significant anti-proliferative activity in HepG2 human hepatocarcinoma and CT26 mouse colorectal cancer cells (Kestwal et al. 2011). The increase in cancer risk due to the deficiency of sulphur amino acids is another indicator for sulphur's anti-cancerogen effect. The deficient sulphur intakes decrease glutathione S-transferase P enzyme. Poor nutrition or supplementation in sulphur also up-regulates homocysteine-clearing enzymes such as cystathionine beta-synthase, methionine synthase, methylene tetrahydrofolate reductase and betain homocyteine methyl transferase, leading to an increase in the proliferation of MCF-7 breast cancer cells (Ryu et al. 2011). Sulphur amino acids decrease homocyteine since the sulphur containing enzymes, cystathionine and cysteine, are produced by sulphur through trans sulfuration. Homocyteine is inflammatory and hence it has got a significant contribution to cancer formation. On the other hand, glutathione and taurine, the important anti-cancerogens, are also procuded from a sulfur containing amino acid, methionine. Not only the production of cystathionine and cyteine, but also vitamins B_{12} and B_6 may decrease the concentration of homocytein by converting it back to methionine through trans methylation. Therefore, any single nucleotide polymorphism that influence folate and vitamin B metabolism can increase homocyteine while decreasing sulfur amino acid concentration, increasing cancer risk (Davis et al. 2005; Grimble 2006).

NITRIC OXIDE/ARGININE
The approach to Nitric Oxide (NO) and arginin matters in cancer nutrition

NO, the free diatomic molecule which is formed from the nitrogen in the guanidine of L-arginine, under the catalytic action of the NOS enzymes, induces S-nitrosylation (the attachment of a thiol group from a cysteine residue to form an S-nitrosothiol, SNO) of the active site cysteines in caspases and other related proteins, leading to inhibition of apoptosis. The S-nitrosothiols formed also leads to the oxidation of thiol proteins which may activate the cell survival (Mannick et al. 2001; Rössig et al. 1999).

Although the association of arginin, NO production and iNOS activity is well studied and documented, the dual action of arginin, NO and iNOS in cancer, 'being cancerogenic or anticancerogenic', still remains a dilemma. The more convincing factors known currently which make arginin, NO and iNOS activity, cancerogenic or anticancerogenic, seem the 'amount' of arginin or NO and the 'long term exposure' to arginin or NO. The reason for the cancerogenic effect of arginin and NO may be due to inflammation that long-term NO induces chronic inflammation which may lead to cancer, like in the mentioned example of colorectal carcinoma progress from ulcerative colitis and increase in NO activity. NO promotes vascular permeability, endothelial cell proliferation and stimulation of angiogenic growth factors, each of which contributes to cancer progress (Lind 2004). One crucial finding about the 'amount' factor which makes NO cancerogenic or anticancerogenic is the down-regulation of the antiangiogenic protein TSP1 by lowe dose of NO (0.1 μM), resulting in the triggering of the progrowth signal, ERK, by phosphorylating it. But all these angiogenic responses can be conversely suppressed by exogenous TSP1. On the other hand, the higher sustained doses of NO donor (1000μM) induce up-regulation or phosphorylation of signaling molecules, p53-Ser-15P and MKP-1, that arrest growth and induce cell death (Ridnour et al. 2005; Roberts 1996; Dameron et al. 1994; Klein-Soyer et al. 1997).

A solid tumor consists of different of tumor cells; fibroblasts, lymphocytes, macrophages, neutrophills and endothelial cells, all may serve as a source of NO. Confirming this, NOS activity may increase in these cells by pro-inflammatory cytokines and hypoxia present in these tumor cells (Rosenkranz-Weiss et al. 1994). Additionally, the highly lipophilic nature of NO makes its transcellular pass easier and its effects stronger between tumor cells and other cell types (Lind 2004).

Tumors require arginine for growth. Normal cells can synthesize arginine from citrulline through arginosuccinase synthase and arginosuccinase lyase but cancer cells can not, since they do not express these enzymes. Therefore, arginine deprivation has gained a using platform as an antineoplastic therapy. NO produced by arginine has also been shown to be in close relation with vascular endothelial growth factor (VEGF) which may also contribute to angiogenesis (Uhlmann et al. 2001). The limitation in arginine in cancer like the avoidance from arginine richest foods; turkey breast, beef, ground red meat, lupin, soybean, nuts, seeds, egg white, peanut, mollusk, chickpea, soy flour, sesame seed, lentil, beans, chicken meat and pork meat (USDA, Pelease 28), may be beneficial during the treatments using VEGF inhibitors; sunitinib, sorafenib, bortezomib, bortezomib and MP0250 combination, MG132, MG262, KF58333, 17-AAG, geldanamycin, SNX-2112, honokiol, thapsigargin, bafilomycin A1, budesonide, brefeldin A, monensin, ritonavir, bevacizumab, ranibizumab, fulvestrant and vandetanib combination, tamoxifen, clomiphene, nafoxidine, [ICI82,780], metformin, paclitaxel, tunicamycin and PTK787/ZK222584 (vatalanib), since arginine may be contraindicated due to its VEGF stimulating effect with the VEGF inhibitors.

The mentioned close relation of NO with chronic inflammation and NO's contributing effect to cancer process via the chronic inflammation may also be confirmed by the inflammatory cytokine inductions by NO, like NO_2 (100-300 μM) induced IL-8 expression (Seo et al. 2009; Corriveau et al. 1998). But, these findings should not be evaluated as if NO definitely induces IL-8. The evaluation of the anticancer potential of NO, its relation with inflammatory cytokines like IL-6 and many other cancerogens is closely depend on its previously mentioned 'dose (amount)' and 'time of exposure' factors. In both studies of Seo et al.

(2009) and Corriveau et al. (1998), the doses of NO in the treatments of cell cultures; 100 and 300 μM are lower than the 1000 μM, the amount which was claimed as strongly anti-proliferative by Ridnour et al. (2005). Another big dilemma about the association of NO and cancer appears at this point that, a very limited number of studies appear to apply different doses of NO, some prefer very low doses which induce proliferation and inflammatory cytokine production while a few of others use very high doses of NO, at least higher than 400 μM. But, the only crucial step we currently reach about NO seems the dual potential of the molecule, which is determined strongly by its 'amount' and 'time of exposure'. The lower doses may lead a cancerogen NO whereas the higher doses (≥400 μM) may result in NO with a strong anticancerogenic and antiproliferative effect!. Until these 'amount', 'time of exposure' and 'cell type' (in cancer cell cultures) associations with NO become more clear, arginin and NO supplementations, not only in cancer nutrition, but also in sports (e.g. bodybuilding), should be cautiously concerned. It may be useful to advice to determine the approach in cancer treatment and nutrition, based on the 'amount' of NO. The higher amounts of NO like ≥400 μM may inhibit IL-8 and, the mentioned IL-8 inhibitors may be advised to be combined with the mentioned arginin rich foods. Otherwise, IL-8 inhibitors should be administered without arginin rich foods as mentioned above. As a result, IL-8 inhibitors; reparixin, lidocaine, SC-514, PS-341, MG132, SB-225002, imatinib, erythromycin, clarithromycin, GO6976, diaryl imidazoles, azelastine, celastrol, sunitinib, sorafenib, cisplatin, tetrandrine, thapsigargin, ritonavir, metformin, tamoxifen and honokiol, may show stronger anticancer effect if a diet free from arginin richest foods; turkey, beef, ground meat, lupin, soybean, nuts, seeds, egg white, peanut, mollusk, chickpea, soy flour, sesame seed, lentil, beans, chicken and pork, since arginin in high amounts in these foods may decrease the anticancer potential of the mentioned drugs by inducing IL-8 expression, in case of poor NO condition (≤400 μM). Another study which confirms the importance of 'amount' criteria to determine the character of NO as cancerogenic or anticancerogenic, is belong to Siednienko et al. (2011) and Ridnour et al. (2005). The authors point out to the inhibition of anti-cancerogenic and anti-inflammatory effects of NO provided that

its amounts are 500 or 1000 μM. Based on the same approach, as long as the NO amounts are not higher than 400μM, the IL-6 inhibitors; tocilizumab, sunitinib, sorafenib, metformin, radicicol, 17-AAg, monensin, brefeldin A, raloxifene, bortezomib, siltuximab, honokiol, curcumin, HO-1 inhibitors; carbon monoxide, biliverdin and free iron, tin (IV) protoporphyrin IX (ZnPP), zinc (II) deuteroporphyrin IX-2,4-bisethyleneglycol, imidazole-based compounds (8,9,10R,10S,11,12,13,3), caveolin-1, calcineurin, siRNA, metformin, tin-mesoporphrin (znPP), PEG-ZnPP (pegylated zinc protoporphyrin),OB-24([2-(4-bromophenyl) ethyl]-2-[1H-imidazol-1-y-yl)methyl]-1,3-dioxolone hydrochloride), should better be administered without the arginin rich foods. Conversely, the arginin richest foods may be useful, provided that the administered NO amounts are ≥400 μM, 500 or 1000 μM. Confirmingly, the necessity of 'being high dose' to make NO anticancerogenic and anti-inflammatory, does also work for COX-2, according to the findings of Park et al. (2003). L-argine as in the amounts of ≥ 440 μM inhibits tumor cell migration as ≥ 14.2 % in various cancers while decreasing COX-2 levels. Provided that arginin is administered as >400 μM, 500 μM or 1000 μ, these administrations may enhance the anti-cancer potential of COX-2 inhibitors like; sunitinib, celecoxib, magnolol, honokiol, eugenol, rofecoxib, nafroxen, dexamethasone, hydrocortisone, beclamethasone diproprionate, by forming a synergy via the inhibition of COX-2.

Another important finding about the anticancer potential of the 'high dose nitric oxide' is the apoptosis induced by the 1.5 mmol/L (1500 μM) NO treatment of RAW 264-7 cells (macrophage cell culture) as compared with the low dose, 0.1 mmol/L NO treatment which results in the blockage of apoptosis. The main reason in this apoptosis by the 'high dose of NO' was found via the induction of a transcription factor, CAAT/enhancer binding protein (C/EBP) homologous protein (CHOP) (Mori 2007), the unfolded and malfolded client protein which imposes a stress on endoplasmic reticulum (ER) and activates GADD34, the pro-apoptotic protein which interferes with the binding of TRAF6 (E3 ubiquitin-protein ligase) to anti-apoptotic protein Akt, leading to retension of Akt and as a result, leading to apoptosis (Farook et al. 2013). Therefore, 'the high dose argini/NO' may enhance the anticancer

potential of the Akt inhibitors; LY29002, SF-1126, NVP-BEZ235, XL147, XL765, ISC,4, GSK690693, MK-2206, fusedpyrimides, PIP3, GDC,0941, celecoxib, UCN-01, BX,912, BX-320, CCT128930, GDC-0068, perifosine, AT13148, PF-04691502, A47867 and triciribine, by forming a synergy to inhibit Akt.

It should be noted that curcumin (e.g. *Curcuma longa*, cinnamon and cinnamon containing foods) may be helpful to the 'high dose arginine/NO' treatments by inducing CHOP (Cao et al. 2013) while apigenin (e.g. grapefruit, parsley, onion, orange, tea, wheat, sprout, chamomile, arthicoke, Chinese cabbag bell pepper, garlic, celery, guava, french peas, kadok, belimbi fruit, snake guard and wolfberry) should be avoided during the same treatments since the flavon conversely inhibits the pro-apoptotic chaperon, CHOP (Jeon et al. 2015). The combination of the two of the most common anticancer drugs; doxorubicin and gamitrinib, has also been determined to induce CHOP (Park et al. 2014) and thus, the treatment using doxorubicin and gamitrinib as combined with 'high dose arginin/NO' therapy and coumarin and/or coumarin rich food consumption, may be another promising anticancer approach, waiting for trial, to be highlighted.

One of the anticancer effects of 'high dose arginine/NO' treatment (600 μM), is the induction of the proaopototic proteins, BIM proteins as the member of Bcl-2 family of apoptotic regulatory proteins accompanied with the opening of mitochondrial permeability (Harada anjd Grant 2012), using the transition pores, releasing cytochrome c by caspase activation. Moreover, the important detail, but also a significant proof for the cancerogenic effect of the 'low dose-NO' rather than being anticancerogenic is the decrease in BIM proteins due to 5-20 μM NO and as a result, an increase in cell survival (Zhai et al. 2013). Once more, it may be crucial to remind that the considered results of the two studies belong to Jin et al. (2006) and Zhai et al. (2013) are due to the 'difference in the dose of NO' that high dose of NO/Arginin has anticancerogenic effect whereas the low dose has the opposite.

A new important novel approach waiting to be highlighted may be the combined use of 'high dose NO/arginine' with the administration of a histone deactylase inhibitor, like suberoyl bis-hydroxamic acid (SBHA) which is informed to upregulate Bim (Chen et al. 2009). Such

a new approach involving the combined use of the 'high dose NO/ arginine' and a histone deactylase inhibitor' may benefit from a rich nutrition in arginine and curcumin, foming a synergy to induce the proapoptotic proteins, Bim.

The caspase activity (involving caspase 3, 2, 7 and 9) increases the release of cytochrome c and ROS through the mitochondrial dysfunction and endoplasmic reticulum stress, following the induction of BIM proteins by NO, again, as in a dose depended manner (provoking both apoptosis and necrosis at 1000 μM as compared with the weaker apoptotic effect of 10-100 μM) (Uchiyama et al. 2002; Wei et al. 2000; Rodriguez-Serrano et al. 1012; Moriya et al. 2000). Therefore, the anticancer drugs that increase ROS and caspase activity, like; sunitinib, sorafenib, tetrandrine, cisplatin, bortezomib, vorinostat, MG-132, metformin, thapsigargin, tunicamycin, 17AAG, DBeQ, ritonavir and brefeldin A, may benefit from the 'high dose NO/arginine' treatment as combined, since both the anti-cancer drugs and NO/arginine increase caspase activity and ROS while leading to the cytochrome c release.

Under the highlight of a very limited number of studies as related to the Hedgehog signaling which induces angiogenesis and cell proliferation, L-arginine has been informed to trigger Hedgehog signaling (Ozturk et al. 2009). But, the use of only three different arginine amounts which were below 25 nmol/g may be an important limitation of the study, since there is a possibility that greater levels of apoptosis could have been yielded to inhibit Hedgehog if the higher doses had been used.

Because of the cloudy status of 'Hedgehog signaling and NO/ arginine' association and the lack of the researches to highlight the effect of the 'high-dose NO/arginine'treatments on cancer via the Hedgehog signaling (as compared with the low dose NO/arginine), either arginine rich food consumption or nitric oxide treatments should better be avoided, in particular during the treatments with the Hedgehog inhibitors; SANT1-SANT4, CUR-61414, HhAntag-691, GDC-0449, saridegib, phthaladines, mukul, guggulsterone, itraconazole, NVP-LDE225, TAK-441, XL-139, HTS piperidines, MRT-92, MRT-83, PF-04449913, N-acylethanolamides, endocannabionids, IPI926, BMS-833923, LEQ506, GANT61, ribotnikinin, HPI1-4, 2-acylglycerols and 2-alkylglycerol.

Another important Drug and Food interference about NO/ arginine regardless of the amount is the association of NO/arginine with FOXO3, the proapoptotic proteins on which NO has often been shown as inhibitory (Potente et al. 2005; Borniquel et a. 2010). So, the following FOXO3 inducers; metformin, doxorubicin, nipradilol, timolol, melatonin, withaferin A, bortezomib, vorinostat, tunicamycin, paclitaxel, geldanamycin, cisplatin, AZD5363 and 5-aza-2-deoxycytidine, may be contraindicated with NO-donors, NO/arginine treatments and arginine rich foods, e.g.turkey breast, beef, ground meat, lupin, soybean, nuts, seeds, egg white, peanut, mollusk, chickpea, soy flour, sesame seed, lentil, beans, chicken meat and pork meat.

Nitric oxide, the endogenously produced gas, is synthesized by the enzymes; NOS1 (nitric oxide synthase 1) from neuronal tissue, NOS3 from neurons and endothelial cells and NOS2, the inducible calcium-independent isoform (Choudhari et al. 2013). Unlike others, the induction of NOS2 results in continuous production of nitric oxide (Moncada et al. 1991). This enzyme can produce much higher NO concentrations for hours and even days. But, much more important point when cancer is concerned is the close relation between NOS2 and p53, the tumor suppressor gene. The gene is an important regulator of NOS2 and it inhibits NOS2 when it senses raised cellular NO. The mentioned opposite interaction between p53and nitric oxide may indicate to two important possibilities. First, the people without cancer may suffer from the high dose NO/arginine supplementations, treatments or arginine rich nutrition since the intakes of high amounts of arginine for long periods may inhibit p53 and thus, may increase the vulnerability to cancer. This detail may be useful to consider, especially in one sided advertisements of arginine supplements which only impose the immune boosting effect of the amino acid. Not only the higher fat content but also the rich arginine content of animal origin products may be one of the reasons for the higher incidence of various cancers due to high consumption rate of animal origin products as a result of the inhibition on p53 because of the excess levels of NO. The second important point which has not been highlighted yet is the possibility of the inhibition of mutant p53 in cancer by the high dose NO/arginine. The higher levels of NO/arginine may overactivate p53 or mutant p53 in cancer. Until the effect of the

higher dose NO/arginine treatments on mutant p53 is clarified, either the high dose NO/arginine treatments or arginine rich food consumptions/ supplementations should better be avoided during the treatments which administer mutant p53 inhibitors, e.g. suberoylanilide, hydroxamic acid, panobinostat, PCI-24781, luteolin, EGCG, CP-31398, YK-3-237, trichostatin A, chidamide, LAQ824, sirtinol, salermide, FR901228, AICAR, NSC59984, tubacin and N-2.

NO's association with cancer may form via inflammation like ulcerative colitis induces by NO generation and increase and colorectal carcinoma while inhibition of NO production improves the colitis (Cross and Wilson 2003; Lagares-Garcia et al. 2001).

The fact that effect of nitric oxide on cytokines are different necessitates to create specific strategies in the determination of food and drug combination. 300 μM No inhibits the release of IL-6 while up-regulating the release of TNF (Deakin et al. 1995) which may be evaluated as another cancer proof for the anticancer potential of the gas. The findings of Siednienko et al. (2011) confirms the importance of 'NO/arginine amount' when NO and IL association is concerned that the lower concentrations (≤10 μM) of the gas increases IL-6 levels while the higher concentrations (>100 μM) decrease the cytokine. The findings of Yao et al. (2015) indicates to both; the high dose nitrogen (2000 μM) treatment and the anticancerogenic effect of the high dose nitrogen treatment via the inghibition of Erk, the extracellular signal regulated kinase which acts in cell proliferation and survival. Although, there seems a great possibility for the anticancer effect of the high dose arginine treatment as indicated above, one study claims the induction of fibroblast proliferation by the very high dose of arginine (6000 μM) by inducing Erk signaling (Fujiwara et al 2014). Fibroblasts are associated with cancer cells at all stages of cancer progression and their production of growth factors, chemokines and extracellular matrix facilitates the angiogenic recruitment of endothelial cells and pericytes. Therefore, they are a key determinant in the malignant progression of cancer and represent an important target for cancer therapies (Kalluri and Zeisberg 2006). Though the study was carried out not in cancer cells, but instead in wound, the significant increase in the fibroblast proliferation in the study appears as completely conflicted with the findings of the

anticancerogen effect of the high dose arginine treatments. On the other hand, while the high dose arginine/NO treatments may increase the fibroblast proliferation, this may be only one side of the case but in the overall, the high dose arginine/NO treatments, via the other mechanisms (the inhibition of IL-6 and IL-8, COX-2, CHOP and induction of Bcl-2, GADD34, ROS and caspase 3, 2, 7 and 9, as previously mentioned), may show the mentioned anticancer effects. More studies may help to highlight the two sides; will the fibroblast increase make the prognosis worse or will it result in an apoptosis?. But, like in the use of Hedgehog inhibitors and FOXO3 inducers, especially in the treatments of cancers, involving fibroblasts, the high dose arginine and NO treatments may be adviced to be avoided until the questions above are answered. Finally, the effect of the high dose of arginine/NO on Erk is also unkown and needs urgent studies. Accordingly, the anticancer treatments using MAPK/ERK inhibitors; vorinostat, ritonavir, radicicol, tamoxifen, geldanamycin, lapatinib, fulvestrant, PD98059, UO126, honokiol and SNX212, may benefit from the foods/plants that similarly inhibit MAPK/ERK signaling; tea, broccoli, apple, strawberries, beans, kale endive, leek, tomato, grapes, blueberries, onion, capsicum pepper, cherry, celery, parsley, plum, apricot, *Gingko biloba*,, *Tilia* spp., *Equisetum* spp., *Moringa oleifera*, *Sophora Japonica* and propolis (the foods which have high kaempferol content), white cabbage, Brussel sprouts, radish, mustard, cauliflower, turnip and Chinese kale (the foods which have high sulforaphane content). But, the combined use of these foods, arginine rich foods and the high dose arginine/NO anticancer treatments, should definitely be avoided from the arginine rich foods; turkey, beef, peanut, ground meat, lupin, soybean, nuts, seeds, egg white, sesame seed, lentil, mollusk, chicken and pork meats, chickpea, nuts and seeds, since the effect of high levels of arginine/NO on MAPK/ERK is still unknown.

Arginine was also informed to increase the phosphorylatrion of the anti-apoptotic proteins, Akt and activate it (Kawasaki et al. 2003). But, the only current study about arginine and its association with Akt used only the low dose (300 μM) of the amino acid. So, urgent studies are needed, particularly until the effect of high dose arginine (>300 μM) treatments on the enzymes becomes clear, it may be smart approach to avoid from arginine/NO treatments or their supplements or arginine/

NO rich foods during the treatments using Akt inhibitors; LY29002, SF-1126, NVP-BEZ235, XL147, XL765, ISC,4, GSK690693, MK-2206, fusedpyrimides, PIP3, GDC,0941, celecoxib, UCN-01, BX,912, BX-320, CCT128930, GDC-0068, perifosine, AT13148, PF-04691502, A47867 and triciribine.

The close interaction between CDK (cyclin dependent kinase), the enzyme which plays a crucial role during cell proliferation in passing from G2 to M phase, and arginine, is another parameter to be concerned in the evaluation of arginin's cancer status. The protein arginine methyltransferase 6 (PRMT6), the coregulator of the gene expression in various cancer types, whose knockdown causes G1-phase arrest induces senescence while up-regulating the cell cycle regulator CDK inhibitor gene p21. But, the overexpression of PRMT6 leads to reduced levels of senescence (Stein et al. 2012). The difficulty for the evaluation of the findings in the study of Stein et al. (2012) is due to the use of PRMT6, the enzyme containing arginine, as the main arginine source which is already exist in normal and cancer cells. However, neither a high dose arginine nor low dose arginine treatments were studied by the authors. Therefore, although arginine as in the form of PRMT6 whose overexpression inhibits senescence, the study does not give answer for any change in PRMT6 and senescence levels by the high arginine/NO treatments. Because of the mentioned ambiguity about the effect of high and low dose arginine treatments on PRMT6 and CDK, it may be advisable to avoid the high dose arginine/NO treatments, their supplementations or arginine/NO rich foods like; turkey, beef, peanut, ground meat, lupin, soybean, nuts, seeds, egg white, sesame seed, lentil, mollusk, chicken and pork meats, chickpea, nuts and seeds, especially during the anticancer treatments by CDK inhibitors; palbociclib, fulvestrant, tamoxifen, honokiol, MCS-C2, flavopiridol, brefeldin A, ritonavir, thapsigargin, MU6140, 17-AAG, purine olomoucine, purvalanol B, roscovitine, ZK304709, PD-0332991, SNS-032, SCH-727965, AZD5438, AT7519, RGB-286638, P1446A-O, P-276-00, PD-0332991, PHA-848125, R547 and RGB-286638.

One of the anticancer effects of the amino acid may be the decrease in the activities of two muscle-specific MMP-2 and MMP-9 (Hnia et al. 2008), the enzymes which degrade the surrounding extracellular

matrix (ECM) to make way to the vascular system and angiogenesis. The level of arginine in the study may be accepted as high since 200 mg/Kg arginine was directly injected as intraperitoneal instead of oral administration. Because of the mentioned anticancerogenic effect of the high-dose arginine treatment by decreasing metalloproteinase activity, the metalloproteinase and collogenase inhibitors; AG3340, BAY12-9566, CGS27023A, marimastat, bryostatins, lapatinib, BB-94, tamoxifen, radicicol, UO126, metformin, celecoxib, honokiol, 17AAG, raloxifene, tetrandrine, naproxen, buprofen, rofecoxib, dexamethasone, bleomycin, hydrocortisone, methylprednisolone, MG132, vorinostat, tunicamycin, brefeldin A, arfaptin 1, lactacystin and trichostatin A, may benefit from the high-dose arginine/NO treatments/supplementations or arginine/NO rich foods. Not only arginine/NO rich foods; turkey, beef, peanut, ground meat, lupin, soybean, nuts, seeds, egg white, sesame seed, lentil, mollusk, chicken and pork meats, chickpea, nuts and seeds, but also kaempferol rich foods/plants; tea, broccoli, blueberries, cherry, strawberries, beans, leek, tomato, endive, kale, onion, grapes, parsley, plum, apricot, capsicum pepper, celery, *Gingko biloba*, *Tilia* spp., *Equisetum* spp., *Morinja oleifera*, *Sophora janonica* and propolis, may also be useful since kaempferol like arginine/NO, decreases metalloproteinase and collogenase activity, as previously mentioned in its related part. An important note, as in close link with arginine and metalloproteinase association, is the probability that the high dose arginine/NO treatments/supplementations/rich foods during the treatments with MMP inducing anti-cancer drugs; anandamide and EMMPRINCD140 whose side effects which induce MMP, may be lessen.

The addition of arginine (1.0%) into the diet was informed to increase fatty acid synthase (FAS) (Madeira et al. 2014), the enzymes whose activity increase in cancer, but one of the very few number of studies about FAS and arginine association were performed in pigs and the study is not about the high dose arginine/NO treatment. But, the findings may indicate to a great possibility for the anticancer effect of the high dose arginine/NO via the FAS induction. Moreover, the other study about FAS activity and arginine association is on rats support the same findings, claiming the increase in FAS activity by 50 mg

intraperitoneal injection of arginine (Mohan and Das 2000). The lack of the studies on human and cancer exerts the urgent need for the studies to be performed to highlight the association between arginine and fatty acid synthase activity in human subjects with cancer and cancer cell cultures. Yet, FAS inhibitors; oristat, cerulenin, C75, C93, PARP inhibitors, triazoles, tetrazolones, beta-lactones, EGCG, C247, Omega 3 and GSK837149 may be contraindicated if arginine/NO treatments/ supplementations or arginine/NO rich food consumption in extreme amounts are followed during the treatments using the mentioned FAS inhibitors, since arginine may have an opposite effect via the increase in FAS activity, though the number of these studies which claim the increase of FAS activity by arginine/NO are very limited. All of them are on animal subjects or on noncancerous cell/tissues.

The effects of the amino acid on NF-kB, the protein complex that controls transcription of DNA, cytokine production, cell survival and TNF (Tumor Necrosis Factor, a glucoprotein which induces the haemorrhagic necrosis of tumours as depended on conditions) are still not clear. Out of only limited number of studies, Wei et al. (2013) reveals the demethylation of the p65 subunit of NF-kB on arginine 30 (R30) by protein-arginine methyl-transferase 5(PMMT5) whose overexpression acts as an oncogene in many types of cancer. The findings of Vasilijevic et al. (2007) and Paszt et al. (2006) support the findings of Wei et al. (2013) through the activation of NF-kB by the amino acid, though neither of the studies was performed for cancer nor by comparing the low and high doses of the amino acid. The NF-kB inhibitors like infliximab, etanercept, adalimumab, certolizumab, golimumab, emetine, sunitinib malate, bithionol, narasin, tribromsalan, lestaurtinib, bortezomib, 17-AAG, metformin, radicicol, tunicamycin, geldanamycin, ritonavir, honokiol, vorinostat, celecoxib, tetrandrine, naproxen, indomethacin, sulindac, dexamethasone, curcumin, tamoxifen, resveratrol, kaempferol and ashwagandha (Grunz-Borgmann et al. 2015), all of which also inhibit TNF, may be contraindicated with the arginine/NO treatments/ supplements or arginine/NO rich foods because of the inducing effect of the amino acid on NF-kB. Although single dose was applied without comparing the high and low dose of the amino acid, the findings of Xia et al. (2010) which seems currently the only study about the effect

of the amino acid on only TNF, may be important since it claims significantly important inducing effect of arginine on TNF. Besides, the inhibition of TNF, the induction of TNF as another anticancer approach because of the dual action of TNF may benefit from arginine since the amino acid exacerbates TNF-mediated cell apoptosis. Ironically, the inhibition of TNF by suppressing the VEGF induction by TNF has currently been used as one of the anticancer approaches. On the other hand, TNF, the cytokine is produced by various blood cells, such as T lymphocytes or white blood cells (known as macrophages and monocytes, the cells all of which secrete the cytokine as an immune response to form inflammation, like the induction of intracellular Ca_2+ production of reactive oxygen species and chemotaxis, to eliminate the harmful agent. In this second approach which exploits the dual action of the cytokine, 2:4-fluoro-benzoic acid [5-(3-trifluoromethyl-phenyl)-2-furyl] methylene-hydrazide], nicotinic acid [5-(3-bromophenyl)-2-furyl] methylene-hydrazide (Schepetkin et al. 2008) and polyinosinic acid (Campa et al. 2005), may have a better anticancer effect by creating a synergy with the amino acid since the amino acid, arginine, induces TNF, like the mentioned TNF inducers.

1250-5000 μM arginine was informed to induce caspase-3 activation which results in the suppression of the expression of the anti-apoptotic proteins ; Bcl-2 and Bcl-xL (Jang et al. 2002). The findings are crucial since it is another indicator of the significant anticancer potential of the 'high dose arginine/NO' treatments but not the 'low-dose'!!. Costunolide, cisplatin, mitomycin c, garcinol, brefeldin A, valinomycin, piceatannol, kinetin riboside, lipase inhibitor, THL, imiquimod, SC560, romidepsin, ouabain, digoxin, proscillaridin A, borrelidin, sanguinarine, bortezomib, MT-21, ionidamine, K858, saikosaponin A, CIL-102 and prodigiosin, may show stronger anticancer potential if they are administered as combined with the 'high-dose arginine/NO' treatments/supplements or arginine rich food consumption, creating a synergy to induce caspase.

The crucial problem about arginine is the lack of studies in spite of the possibilities related to its anticancer potential indicated by the mentioned studies. One of the important and crucial notes presently is that unlike some of the bio-active compounds, arginine and I3C are the ones which have not any cohort studies except the mentioned

one below!!. For example, the study mentioned analyses the effect of arginine deprivation while there is no any other study presently about the effect of the mega doses of arginine!!

- 19 patients/42-74 years of age/alcohol not adjusted, smoking not adjusted/>680 d follow up/the amino acid-degrading enzyme arginine deiminase conjugated to polyethylene glycol to lower plasma arginine was administered/the arginine deprivation decreased the risk of hepatocellular carcinoma (Izzo et al. 2004).

APIGENIN

Apigenin, the flavon is the compound which forms after the glycosyl group (a free radical which is obtained by removing hydroxyl group from the cyclic form of a monosaccharide) on a glycoside (a molecule in which sugar is bound to another group via a glycosidic bond) is replaced by a hydrogen atom. The flavon is chemically known as 4,5,7-trihydroxyflavone ($C_{15}H_{10}O_5$) abundantly present in grapefruit, parsley, onion, orange, tea, wheat sprout, chamomile (Shukla and Gupta (2010), artichoke (Wang et al. 2003), Chinese cabbage, bell pepper, garlic, celery, guava (Horinaka et al. 2006), French peas, kadok, belimbi fruit, snake gourd and wolfberry (Miean and Mohamed 2001).

Death receptors (DR1-DR6) which are belong to the tumor necrosis factor receptor (TNF) family engage intracellular apoptotic pathways upon binding of their ligands of the TNF family. TRAIL, also known as Apo2L is a TNF family ligand that binds on the death receptors, DR4 (also known as TRAIL-R1) and DR5 (also known as TRAIL-R2) activates apoptosis in cancer cells (Wiley et al. 1995). DR5 and DR4, the death receptors of TNF-related apoptosis-inducing ligand (TRAIL) have become one of the novel targets since TRAIL activates apoptosis through the death receptors DR5 and DR4. Currently, some small molecules that directly target DR5 to initiate apoptosis in human cancer cells like Smac, the antagonist for inhibitor of apoptosis protein DR5 and Bioymifi to induce DR5 aggregation have been introduced (Wang et al. 2013; Takeda et al. 2007). But, the apoptotic pathway which is formed by the binding of TRAIL (TNF family ligand) to the death receptors; DR4 and DR5, is no more functional as a result of higher expression of the TRAIL receptors in tumor cells and relatively high levels of decoy receptors in normal cells (Pan et al. 1997). For this reason, TRAIL targeting strategies; the recombinant human TRAIL (rh-TRAIL) and monoclonal antibodies (MAbs) against DR4 and DR5 (humanized mouse MAb and fully human MABs) (Lawrence et al. 2001; Adams et al. 2008; Mody 2013) have currently gained popularity as one of the novel anticancer approaches. On the other hand, zerumbone (isolated

from wild ginger, Zingiber zerumbet smith), is a TRAIL-induced apoptosis potentiator through the up-regulation of DR4 and DR5 expression and the down-regulation of cFLIP, an anti-apoptotic protein and resistance factor which suppresses TNF-α (Safa 2012; Yodkeeree et al. 2009) with a very little or no cytotoxic effect on normal cells. TRAIL, tumor necrosis factor induced apoptotic ligand/DR5, DR4 inducers; zerumbone (isolated from wild ginger, *Zingiber zerumbet smith*) 15-deoxy-Prostaglandin I2 (15dPGJ2) (su et al. 2008), sunitinib (Teng et al. 2013), honokiol (Lai et al. 2014), thapsigargin (Huang et al. 2004), cisplatin (Blanarova et al. 20119, paclitaxel (Hunter et al. 2011), brefeldin A, epothilone B, vinblastine (Yamaguchi and Wang 2004), metformin (Tanaka et al. 2015), bortezomib (Liu et al. 2007), vorinostat, rh-TRAIL and mouse MAb (Frew et al. 2008) are the anticancer agents/ drugs whose DR5 induced effects are confirmed by the the studies of the researchers in the parentheses and thus the anticancer potential of the mentioned anticancer drugs/agents may be enhanced if the apigenin rich foods/plants; grapefruit, parsley, onion, orange, tea, artichoke, wheat sprout, chamomile, orange, cabbage, celery, guava, garlic, bell pepper, French peas, Kodak, belimbi, snake gourd and wolfberry are included into the anticancer diet since apigenin also induces DR5 (Osihi et al. et al. 2013; Kim et al. 2013 and Horinaka et al. 2006) and thus may form a synergy with these anticancer drugs/agents to enhance their anticancer potential.

One of the most important and interesting studies defines the flavon as one of the strongest chelators. In the study of Romanova et al. (2001), even at the concentration of 1 microM, apigenin exhibits the highest DNA protective effect against free radicals generated by H_2O_2 resp. Fe2+ as compared with luteolin and quercetin. The chelating activity of the flavon has also been confirmed by Mladenka et al. (2011) and Middleton et al. (2000). Like quercetin and many other flavonoids, the capability of apigenin to bind Fe and other minerals may enhance the anticancer effects of STEAP inhibitors and TFR binders which inhibit the cancerous and oxidant ferrous (Fe^{2+}) form of iron. These agents namely; mouse IgG2ak MAbs92.30, mouse IgG2ak mAbs120.545, mouse Anti-TfR1 antibody, monoclonal [TFR-01], pectocin M1 and M2, mouse anti-TfR1 antibody, monoclonal [C2][(M-A712)], human

TfR biotinylated antibody, ch128-1Av, may have stronger contribution to cancer protection and tumor inhibition if administered as combined with an anticancer diet rich in apigenin containing foods like; grapefruit, parsley, onion, orange, tea, artichoke, wheat sprout, chamomile, orange, cabbage, celery, guava, garlic, bell pepper, French peas, Kodak, belimbi, snake gourd and wolfberry, in addition to the quercetin rich foods in similar effect as mentioned in the related part of quercetin.

The flavon's inhibitory effect on COX-2, the enzyme which produces inflammatory and cancerogen hormones, may be one of its contributions to cancer protection and tumor inhibition. Confirming this, skin cancer in mouse, induced by dimethylbenzanthracene (DMBA) and 12-O-tetradecanoylphorbol-13-acetate (TPA) was inhibited by the flavon (Van Dross et al. 2005) and the initial reason for the inhibition on the cancer was claimed as the significant inhibitory effect of the flavon on COX-2.

The inducible Nitric Oxide Synthase (iNOS) which is expressed to produce nitric oxide (NO) after long hours or long days while NO is considered as the modulator of angiogenesis and metastasis (Kroncke et al. 1998;) based on the findings using a mouse model by the increase in 8-nitroguanine and 8-oxo-7,8-dihydro-2'-deoxyguanosine (8-oxodG) (Ding et al. 2005). The inhibition of both inflammatory and cancerogen enzymes, COX-2 and iNOS by the flavon (as concentration depended between 0.5-50 μM) (Raso et al. 2001; Liang et al. 1999; Ha et al. 2008 and Farkas et al. 2015) may enhance the chemotherapeutic effects of the novel iNOS inhibitors, namely; L-arginine, L-canavanine, L-NAMA (NG-nitro-L-arginine methyl ester hydrochloride), L-NNA (L-NG-nitroarginine), N6, NG-dimethyl-L-arginine, L-NIL [L-N6-(1-iminoethyl) lysine dihydrochloride], NILT (N6-iminoethyl-lysine tetrazoleamide), L-NIO [N(5)-(-(-iminoethyl)-L-ornithine], vinyl-L-NIO, AMT(2-amino-5,6-dihydro-6-methyl-4H-1,3-thiazine), L-thiocitrulline, S-methyl-L-thiocitrulline, N-propyl-L-arginine, 1400W, A-guanidiglutaric acid, S-(2-aminoethyl)isothiourea, EIT hydrobromide, Mercaptoethylguanidine, S-ethylisothiourea, S-methylisothiourea, 1,3-PBIT) [1,3-S,S-1,4-phenylenebis (1,2-ethanediyl)bis-isothiourea], 1,4-PBIT, Aminoguanidine, 2-imino-4-methylpiperidine, TRIM (1-[2-trifluoromethylphenyl]

imidazole, 7-nitroindazole, 3-bromo-7-nitroindazole and BYK-191023 dihydrochloride (2-[2-(4-Methoxy-2-pyridinyl)ethyl]-1H-imidazol [4,5-b] pyridine dihydrochloride) (Janakiram and Rao 2012). That the flavon inhibits COX-2, in adiition to iNOS, may improve the anticancer potential of the COX-2 inhibitors, like; sunitinib, celecoxib, magnolol, honokiol, eugenol, rofecoxib, nafroxen, dexamethasone, hydrocortisone, beclamethasone diproprionate. Briefly, the involvement of the flavon rich foods/plants; grapefruit, parsley, onion, orange, tea, artichoke, wheat sprout, chamomile, orange, cabbage, celery, guava, garlic, bell pepper, French peas, Kodak, belimbi, snake gourd and wolfberry, may form a synergy with iNOS and COX-2 inhibitors via the inhibition of these enzymes, increasing the anticancer potential of these inhibitors.

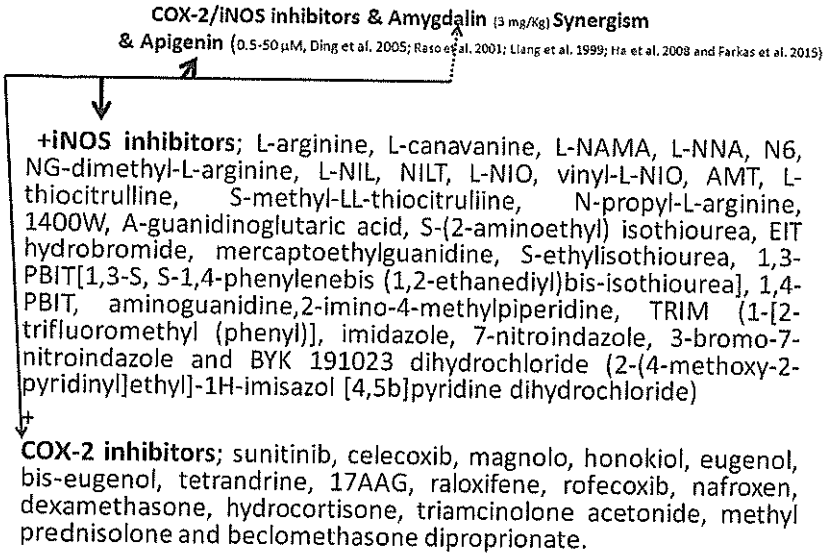


FIGURE 43

Mitogen-activated protein kinases (MAPK) are protein kinases, the enzymes that catalyzes the transfer of phosphate groups from high-energy phosphate-donating molecules to specific substrates. The enzymes are specific to the amino acids; serine, threonine and tyrosine. MAPKs regulate diverse cellular programs by relaying extracellular signals and regulate cell proliferation, differentiation, motility and

survival. The best known MAPKs are ERK1/2 (extracellular signal-regulated kinases 1 and 2), c-Jun amino-terminal kinases 1 to 3 (JNK 1 to -3), p38 (α, β, Υ, and δ) and ERK5. These MAPKs also regulate other substrates or protein kinases (MAPKAPK) namely, the p90 ribosomal S6 kinase (RSK), the mitogen-and stress-activated kinase (MSK), the MAPK-interacting kinase (MNK), the MAPK-activated protein kinase 2/3 (MK2/3) and MK5 (also known as p38-activated protein kinase, PRAK) act importantly in the regulation of nucleosome and gene expression, mRNA stability, cell proliferation and survival (Cargnello and Roux 2011). The MAPK pathways are activated by cytokines, hormones, oxidative stress and endoplasmic reticulum stress while persistent activation of the JNK or p38 signaling is involved in cancer development and progression (Bubici and Papa 2014; Takahashi et al. 2013; Wagner and Nebreda 2009) while both MAPKs regulate the activity and expression of the inflammatory proteins which may function as potent cancer promoters. On the other hand, inhibition of p38 and JNK activates caspase-3 so that this activation degrades ADP-ribose polymerase protein, the protein to repair DNA, and hence, programs apoptosis (Avisetti et al. 2014). Thus, inhibition of MAPKs, especially, the inhibition of JNK and p38, has appeared as another novel target in cancer treatments and prevention. The JNK/p38 inhibitors; SP600125 (Bennett et al. 2001), piceatannol (Kim et al. 2008), CC-401 (Vasilevskaya et al. 2015), RWJ 67657 (Antoon et al. 2012), PKR inhibitors, e.g. imoxin, 2-AP (Nakamura et al. 2014), bentamapimod (JNK inhibitor AS602801) (Palmer et al. 2012), AEG3482 (Salehi et al. 2006), BI78D3 (Stebbins et al. 2008), JNK-IN-8 (Zhang et al. 2012), SU3327(Jang and Javadov 2014), may exhibit stronger anticancer potential if they are administered during an anticancer diet rich in apigenin containing foods since the flavon similarly inhibits MAPKs; p38 and JNK (Lv et al. 2014; Liu et al. 2011; Liao et al. 2014 and Ha et al. 2008).

'Cyclin Dependent Kinase's (CDKs), the protein family which has a vital role in the regulation of the cell cycle, transcription and mRNA processing. Cell cycle progression through each phase is regulated by heterodimers which are formed by CDKs and therefore de-regulation of cell-cycle control due to aberrant CDK activity appears as a common

feature of cancer (Canavese et al. 2012). The hyperactivity of CDKs is one of the mechanisms of the hyper-proliferation in cancer. So, inhibition of CDKs by inserting small molecules into the ATP binding pockets of these kinases has emerged as a potential therapy method for cancer (Sharma et al. 2008; Roberts et al. 2012). Especially, the inducing effect of the CDKs; CDK4 and CDK6 in the G1 phase of the cell cycle (Asghar et al. 2015) indicates to the important potential via the inhibition of CDKs as a novel approach in cancer treatments. On the other hand, apigenin causes a significant decrease in cyclin B1, the regulatory protein which is involved in mitosis. Cyclin B1, making a complex with CDK1, initiates mitosis through the chromosome condensation, nuclear envelope breakdown and spindle pole assembly. Besides, the complex promotes several of the events of early mitosis. What seems vitally important at this stage is that apigenin not only decreases cyclin B1 but also CDK1, resulting in a marked inhibition of CDK kinase activity (Yin et al. 2001). The CDK inhibition and G2/M phase cell cycle arrest by the flavon have also been confirmed by Shukla and Gupta (2006), Shi et al. (2015), Ujiki et al. (2006), Shi et al. (2015) and Li et al. (2009). The mentioned effect of the flavon may enhance the anticancer potential of the most common novel CDK inhibitors; aloisine (Mettey et al. 2003), [RP 106, 7-n-Butyl-6-(4-hydroxyphenyl)[5H]pyrrolo[2,3-b] pyraizne], aloisine A [RP 107, 7-n-Butyl-6-(4-hydroxyphenyl)[5H] pyrrolo[2,3-b]pyraizne] (Rowe et al. 2010), alsterpaullone [9-Nitro-7, 12-dihydroindolo-[3,2-d][1]benzazepin-6(5H)-one] (Lahusen et al. 2003), 3-Amino-1H-pyrazolo[3,4-b]quinoxaline (Ortega et al. 2002), 3-ATA(3-amino-9-thiol[1OH]-acridone) (Diccianni et al. 2004), Benfluorene [Ethyl-(6-hydroxy-4-phenylbenzo[4,5]furo[2,3-b] pyridine-3-carboxylate; 1-Aza-9-oxafluorene5a] (Brachwitz et al. 2003), bohemine [6-benzylamino-2-(3-hydroxypropyl-amino)-9-isopropylpurine] (Liskova et al. 2012), 2-bromo-12,13-dihiydro-5H-indolo[2,3-α]pyrrolo[3,4-c]carbazole-5,7(6H)-dione (Zhu et al. 2003), CGP74514A [N-(cis-2-aminocyclohexyl)-N-(3-chlorophenyl)-9-ethyl-9H-purine-2,6-diamine] (Dai et al. 2002), 3-(2-chloro-3-indolymethylene)-1,3-dihydroindol-2-one (Cheng et al. 2012), compound 52 (Gray et al. 1998), CVT-313[6-(4-methoxybenzylamino-2-[bis(2-hydroxymethylamino)]-9-isopropylurine] (Brooks et al. 1997),

9-cyanopaullone [9-cyano-7,12-dihydroindolo-[3,2-d]benzazepin-6[5H]-one] (Gussio et al. 2000), debromohymenialdisine [DBH;4-(2-amino-4-oxo-2-imidazolin-5-ylidene)-4,5,6,7-tetrahydropyrrolo[2,3-c] azepin-8-one] (Meijer et al. 2000), Elbfluorene [3-acetyl-6hydroxy-4-phenylbenzol[4,5]furo[2,3-b]pyridine; 1-Aza-9-oxafluorene 5b] (Murai et al. 2009), Fascaplysin (dehydroluffarielloide diacid monoanion) (Bharate et al. 2012), 10Z-hymenialdisine[4-(2-amino-4-oxo-2-imidazolin-5-ylidene)-2-bromo-4,5,6,7-tetrahydropyrrolo azepin-8-one] (Meijer et al. 2000), hymenidin[2-debromooroidin](Kobayashi et al. 1986), indirubin-3-monoxime (C16H11N302) (Perabo et al. 2006), N-6-(delta2-isopentenyl)-adenine[6-Y,Y-dimetylallylamino) purine] (Schulze-Gahmen et al. 1995), kenpaullone [9-bromo-7,12-dihydroindolo-[3,2-d]benzazepin-6(5H)-one] (Zaharevitz et al. 1999), NU2058 [O6-cycloexylmethylguanine](Rigas et al. 2007), olomoucine[6-benzylamino-2-(2-hydroxyethylamino)-9-methylpurine] (Boutis et al. 2006), PNU 112455A.HCl [N4-(6-aminopyrimidin-4-yl)-sulfanilamide. HCl)](Knockaert et al. 2002), purvalanol A[6-[(3-chloroanilino]-2(1R)-isopropyl-2-hydroxyethylamino)-9-isopropylpurine] (Hikita et al. 2010), roscovitine [6-benzylamino-2-®-[(1-ethyl)-2-hydroxyethylamino]-9-isopropylpurine] (Huber and O'Day 2012), staurosporine (C28H26N403) (Antonsson an Persson 2009), SU9516[3-[1-(3H-Imidazol-4-yl)-meth-(Z)-ylidene]-5-methoxy-1,3-dihydro-indol-2-one] (Moshinsky et al. 2003), TG02 (also known as SB1317)(C23H24N4O) (Goh et al. 2012), sorafenib (Wang et al. 2010), toyocamycin (Park et al. 1996), bortezomib (which also blocks the activation of CDK by docetaxel as one of the side effects of the anticancer drug) (Canfield et al. 2006), 17 AAG (Zhang et al. 2010), radicicol (Chanmugam et al. 1995), paclitaxel, NU6140 (Pennati et al. 2005), tetrandrine (Lee et al. 2002), metformin (Fujihara et al. 2015), honokiol (Fan et al. 2014) and palbociclib (DeMichele et al. 2015), since both the flavon and the CDK inhibitors may form a synergy to inhibit CDK activity and induce G2 arrest.

Although cancer is a very complex disease, most types have common hallmarks which are; self-sufficiency in growth signals, insensitivity to growth-inhibitory mechanisms, evasion of programmed cell death, limitless replicative potential, sustained angiogenesis, invasion and metastasis. Hsp90 is the molecular chaperon that assists cell proteins to

fold properly, stabilizes proteins against heat stress and stabilizes proteins which are required for tumor growth. The chaperon regulates folding and growth by ATP-binding protein binding and dimerizing. Moreover, the chaperon-client proteins play crucial roles in the establishment of the cancer hallmarks above. The chaperon does not modulate its machinery alone but as in close contact with other co-chaperones; Hop (which links together Hsp70 and Hsp90), Flbp52/51 (the chaperon which plays significant role in protein folding), Cyp40 (cyclophilin D or PDID) which catalyzes the cis-trans isomerization of proline imidic peptide bonds), AIP (complex with AhR, aryl hydrocarbon receptor which plays role in cell proliferation), CHIP (ubiquitin ligase), PP5 (phosphatase), Tpr2 (which mediates the retrograde transfer of substrates from Hsp90 onto Hsp70), Sgt1 (forms complex with Hsp90 and subsequently enhance the resistance of cancer cells against immune system), Unc45 (molecular myosin chaperones which are essential for cell division, proliferation and invasion), Tom70 (mitochondrial protein import), p23, cdc37 which are involved the inhibition of Hsp90) and NudC (nuclear migration protein which plays multiple roles in mitosis and cytokinesis). Therefore, the inhibition of Hsp90 and its mentioned co-chaperones has appeared as one of the novel target in cancer treatment. On the other hand, apigenin has a great effect in depleting Hsp90 clients, the substrate proteins which are matured by Hsp90, like kinase hormone receptor and nonsignal transduction clients, the clients that are involved in signal transduction (Wayne et al. 2011; He et al. 2015; Zhao et al. 2011).

Another important effect of the flavon is its inhibitory effect on VEGF expression via degradation of HIFα through interference with the function of Hsp90 (Osada et al. 2004). Similar to the flavon, quercetin, curcumin, ascorbic acid, (-)-Epigallocatechin-3-gallate and sulforaphane inhibit Hsp90 and its co-chaperons (Li et al. 2009; Li et al. 2012; Van Hauwenhuyse et al. 2014; Basak et al. 2008; Aalinkeel et al. 2008; Lee and Chung 2010). On the other hand, resveratrol induces Hsp90 and its co-chaperons, opposite to the mentioned flavon and flavonoids while the effect of I3C, beta karotene, folat, B6, kaempferol and genistein on the chaperon and its co-chaperons is still remains to be unknown and waiting to be highlighted.

Because of the inhibitory effect of apigenin and also quercetin,

curcumin, ascorbic acid, (-)-Epigallocatechin-3-gallate and sulforaphane on Hsp90 and its cochaperons, the foods/planst rich in these flavons/ vitamins like; caper, onion, cocoa powder, cranberries, cherries, green tea, black tea, lettuce, apple, asparagus, green pepper, tomato, broccoli, red grape, apple, banana, grapefruit, spinach, citrus fruits like orange, lemon, white cabbage, red cabbage, cauliflower, Brussels sprouts, radish, mustard, turnip, Chinese kale, cinnamon and Curcuma longa may be beneficial if included in the anti-cancer diet during the treatments with Hsp90 inhibitors; geldanamycin (Miyata et al. 2005), 17AAG (tanespimycin (Powers et al. 2013), 17-DMAG (geldanamycin analog)(Sun et al. 2013), 17-AG (17-amino-17-demethoxygeldanamycin; IP-493)(Lee et al. 2008), trastuzumab, IPI-504 (Scaltriti et al. 2011), radicicol (Schulte et al. 1998), AT13387 (Smyth et al. 2012), PU-H71 (Ambati et al. 2014), AICAR (5-aminoimidazole-4-carboxamide-1-β-D-ribofuranoside)(Meli et al. 2006), herbimycin A (Whitesell et al. 1994), gedunin (Patwardhan et al. 2013), celastrol (Chadli et al. 2009), NVP-AUY922 (Garon et al. 2013), HSP-990 (Menezes et al. 2012), KU135 (novobiocin-derived C-terminal Hsp90 inhibitor) (Shelton et al. 2009), novobiocin (Marcu et al. 2000), macbecin (Martin et al. 2008), ganetespib (Lazenby et al. 2015), MPC-3100 (Yu et al. 2010), benzisoxazole Hsp90 inhibitor (Taldone et al. 2009), 17-GMB-APA-GA (Mandler et al. 2004), 17-AEP-GA (Miekus et al. 2012), 17-DMAP-GA (Jurczyszyn et al. 2014), KW-2478(Nakashima et al. 2010), NVP-BEP800 (Hartmann et al. 2013), B11B021 (Lundgren et al. 2009), nelfinavir mesylate (Kushchayeva et al. 2014), VER-50589 and VER-49009 (Sharp et al. 2007), honokiol (Park et al. 2009) and also cytarabine, carboplatinum, toptecan, vincristine, cyclophosphomide, cisplatin, methotrexate and etoposide, the chemotherapeutic agents which are in synergism with AAG to inhibit Hsp90 (Hawkins et al. 2005) and finally shepherdin, pochonin, radester, PU-3 and PU24FCl (Xiao et al. 2006), the anti-cancer agents whose inhibitory effects on Hsp90 are confirmed by the authors who are referred in the parenthesis, creating a synergy via the inhibition of Hsp90 and its chaperons.

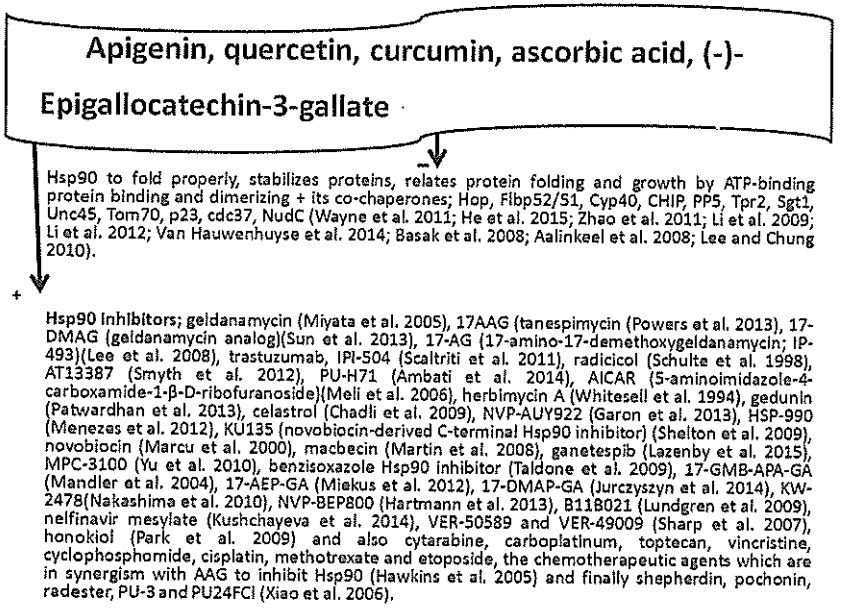


FIGURE 44

Phosphatidylinositol 3-kinase (PI3K), Akt and mammalian target of rapamycin (mTOR) comprises the 3 major functions which are activated by upstream signaling of tyrosine kinases and other receptor molecules (Vivanco and Sawyers 2002). PI3K pathway is a critical signal transduction system which links oncogenes and multiple receptors to many essential cellular functions, especially cell survival, proliferation and growth while the pathway is the most commonly activated signaling pathway in human cancer (Liu et al. 2009). The family of lipid kinases, PI3Ks, acts as the major effectors which downstream of receptor tyrosine kinases (RTKs) and transducer signals from growth factors and cytokines into intracellular messages by generating phospholipids that, in turn activate the serine/threonine kinase Akt, activated tyrosine kinases. Serine/threonine kinases, AKTs, especially Akt 1, 2, 3, also known as PKBα, PKBβ and PKBY, regulate cell proliferation and embryonic development by phosphorylating the OH (hydroxyl) group on the side chain of a serine or threonine amino acid residue in a protein with a phosphate group from ATP (Liu et al. 2009). The

hyperactivation of PI3K and AKT signaling cascades is one of the most common events in human cancers (Thorpe et al. 2015; Fresno Vara et al. 2004; Baselga 2011; Fruman and Rommel 2014; Romano 2013). On the other hand, apigenin inhibits the phosphorylation of p70S6K1, a serine/threonine kinase, which is a down stream blockage of VEGF and HIF-1α expressions (Fang et al. 2005), leading to the tumor inhibition. Apigenin also reduces the phosphorylation of Akt while increasing the binding of FOXO3a (the transcription factor whose deregulation is involved in tumorigenesis) with p27 (a cyclin-dependent kinase inhibitor) which results in GO/G1-phase cell cycle arrest (Shukla et al. 2014; Lee et al. 2008). Therefore, the flavon may enhance the anti-cancer potential of the PI3K and AKT inhibitors. The inhibitors; wortmannin (Teranishi et al. 2009), piceatannol (Kwon et al. 2012), IC-87114 (Billottet et al. 2006), myricetin, quercetin, LY294002, staurosporine (Walker et al. 2015), PIK-75 (Jeong et al. 2014), XL-147 (Foster et al. 2015), WHI-P154, WHI-P131 (Linwong et al. 2010), CAL-101 (Hoellenriegel et al. 2015), GSK2126458 (Knight et al. 2010), Fisetin (Lim et al. 2015), 17-β-hydroxyWortmannin (Zhu et al. 2006), miltefosine, perifosine, NVP-BEZ235, rosiglitazone (Bhatt et al. 2015), SF1126 (De et al. 2013), CH5132799 (Blagden et al. 2014), CAY10505 (Tyagi et al. 2012), quercetin (Gulati et al. 2006), 3, 4, 7-trihydroxyisoflavone (one of the metabolites of daidzein) (Lee et al. 2010), compound 15e (Hayakawa et al. 2006), PIK90 (Cheng et al. 2012), PIK-294 (Knight et al. 2006), GSK1059615 (Markman et al. 2010), PX-866, SF1126 (Garlich et al. 2008; Ihle et al. 2004), NVP-BEZ235, PF-04691502, BGT226, XL765 (Maira et al. 2008), GDC-0941, NVP-BKM120 (Edgar et al. 2010; Ehrhardt et al. 2015; Lonetti et al. 2013), BKM120 (buparlisib) (Geuna et al. 2015), GDC-0032 (talesib) (Edgar 2015), BAY80-6946 (Liu et al. 2013), IPI-145 (Balakrishnan et al. 2015), BEZ-235 (Serra et al. 2008), BYL719 (Fritsch et al. 2014), GDC-0980 (Wallin et al. 2011), PF-05212384 (Shapiro et al. 2015) and also sunitinib, sorafenib (Krusch et al. 2009), Paclitaxel, 17-AAG (Sain et al. 2006), tamoxifen (Chen et al. 2013), BIG1 (a brefeldin A-inhibited guanine nucleotide-exchange protein) (Zhou et al. 2013), MG-132 (Zanotto-Filho et al. 2012), metformin, rapamycin (Zakikhani et al. 2010), fulvestrant (Van Tine et al. 2011), honokiol (Crane et al. 2009), cisplatin (Lee et al. 2005), tetrandrine (Chen et al. 2008), raloxifene

(Kawagoe et al. 2003) and ICI 182,780 (Lam et al. 2009), the anti-cancer agents/bio-active compounds whose inhibitory effects on PI3K and/or mTOR (the mammalian target of rapamycin, a serine/threonine kinase which is a downstream effector of the PI3K/Akt pathway) are proven or confirmed by the researchers in parantheses, may have stronger anticancer potential provided that they are administered during an anticancer diet rich in apigenin, quercetin and daidzein. Because these mentioned bio-active compounds also inhibit PI3K/AKT/mTOR as being similar to the mentioned anticancer agents and drugs. All the mentioned bioactive compounds and anticancer agents/drugs may form a synergy via the inhibition on PI3K/AKT/mTOR pathway. Moreover, curcumin, genistein, folic acid, lycopene, kaempferol, resveratrol, sulforaphane are the other bioactive compounds which similarly inhibit PI3K/AKT/mTOR pathway. Therefore, the involvement of the foods rich in these bioactive compounds in an anticancer diet may also enhance the anticancer potential of the mentioned drugs/agents by forming the same synergy. It should be taken into consideration importantly that, ascorbic acid (vitamin C) and vorinostat activate PI3K (Shukla et al. 2013) and therefore should be avoided during the treatments with the mentioned PI3K/Akt/mTOR pathway inhibitors.

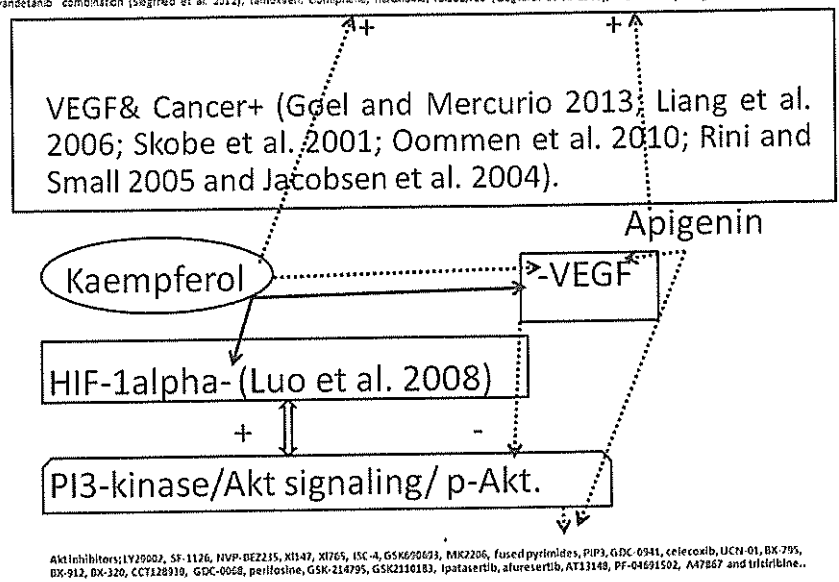


FIGURE 45

The flavon induces caspase-dependent p53-mediated apoptosis (Torkin et al. 2005) and therefore, may enhance the anticancer potential of the anticancer drugs which similarly induce caspace activity, the anticancer drugs namely; costunolide, mitomycin C, garcinol, valinomycin, piceatannol, kinetin riboside, lipase inhibitor, THL (tetrahydroliplastatin), imiquimod, SC560, romidepsin, ouabain, digoxin, proscillaridin A, borrelidin, sanguinarine, MT-21, ionidamine, K858, sikosaponin A, CIL-102 and prodigiosin and also the anticancer drugs which induce ROS production like; sunitinib, sorafenib, tetrandrine, cisplatin, bortezomib, vorinostat, MG-132, metformin, thapsigargin, tunicamycin, 17AAG, DBeQ, ritonavir and brefeldin A.

The flavonoid has also been shown to inhibit ERK (the serine/ threonine kinases which produce anti-apoptotic signals), the anti-apoptotic proteins; Bcl-2, Bcl-xL, STAB (the protein which is activated through phosphorylation of tyrosine 705, in response to various cytokines and growth factors, mediating the expression of a variety of genes in response to cell stimuli and pluripotency, Akt, serine/

threonine kinase which produce anti-apoptotic signals) and NF-kB (Nuclear Factor Kappa-light-chain enhancer of activated B cells, the protein which controls transcription of DNA while its overactivation stimulates cancer) (Zhao et al. 2011). Therefore, the anticancer effects of the anticancer drugs that inhibit NF-kB, namely; emetine, fluorosalan, sunitinib malate, bithionol, narasin, tribromsalan, lestaurtinib, ectinascidin 743, chromomycin A3 and bortezomib, the anticancer drugs that inhibit ERK, like; vitamin C, sulforaphane, genistein, vorinsotat, lapafinib, fulvstrant, PD98059, U0126 and honokiol, the anticancer drugs that inhibit Bcl-2 and Bcl-xL; HA14-1, AT-101, obatoclax, ABT-263, ABT-737, sunitinib, sorafenib, thapsigargin, bortezomib, 17-AAG, vorinostat, honokiol, metformin, tetrandrine, tamoxifen, geldanamycin, radicicol and raloxifen, the anticancer drugs that inhibit Akt, namely; LY29002, SF-1126, NVP-BEZ235, XL147, XL765, ISC-4, GSK690693, MK2206, fused pyrimides, PIP3, GDC-0941, celecoxib, UCN-01, BX-795, BX-912, BX-320, CCT128930, GDC-0068, perifosine, GSK-214795, GSK2110183, Ipatasertib, afuresertib, AT13148, PF-04691502, A47867 and triciribine and finally STAT3 inhibitors; S3I-201, static, STA-21, WP1066, cucurbitacin >B, 5,15-diphenylporphrin (5,15-DPP), niclosamide, auranofin, galiellalactone, kahweol, cepharanthine, SD1008, nifuroxazide, cryptotanshinone, ruxolitinib phosphate, STAT 3 inhibitor VII, sunitinib, sorafenib, bortezomib, guggulsterone, paclitaxel, honokiol, metformin, 17-AAG, vorinostat, romidepsin and tetrandrine, may all be enhanced if the apigenin rich foods in addition to sulforaphane, vitamin C and genistein rich foods are included into the anticancer diet during the treatments with the mentioned anticancer drugs/agents. Because the flavonoid may form a synergy to inhibit NF-kB, Bcl, STAT3 and Akt, with the mentioned bio-active compounds and the anticancer drugs.

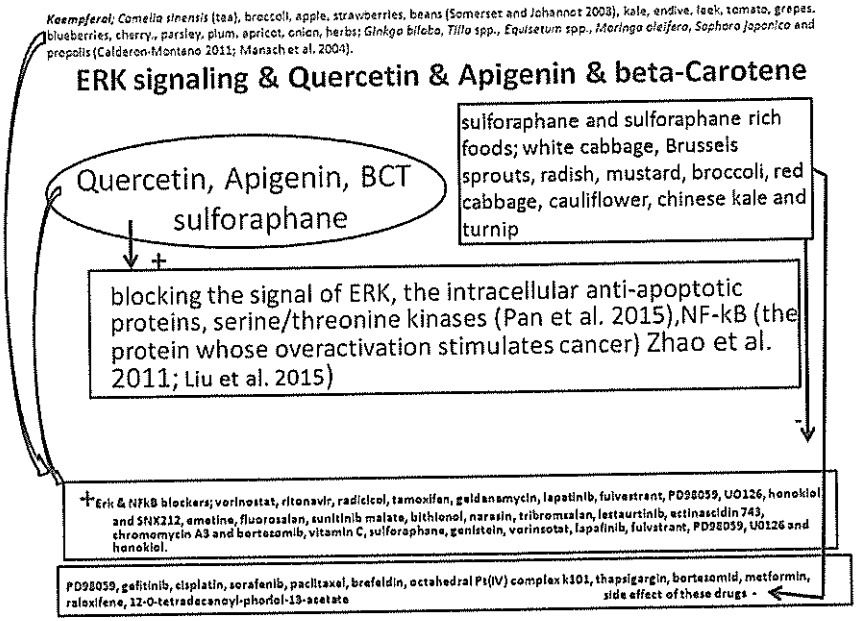


FIGURE 46

The dietary flavonoid's one other significant anticancer effect is due to its inhibitory effect on VEGF (Vascular Endothelial Growth Factor, the signal protein to stimulate vasculogenesis, the process of blood vessel formation and angiogenesis) (Fang et al. 2005; Liu et al. 2005). Thus, the apigenin rich food involvement into the anticancer diet during the treatments with the VEGF inhibitors; sunitinib, sorafenib, bortezomib, bortezomib and MP0250 combination, MG132, MG262, KF58333, 17-AAG, geldanamycin, SNX-2112, honokiol, thapsigargin, bafilomycin A1, budesonide, brefeldin A, monensin, ritonavir, bevacizumab, ranibizumab, fulvestrant and vandetanib combination, tamoxifen, clomiphene, nafoxidine, [ICI82,780], metformin, paclitaxel, tunicamycin and PTK787/ZK222584 (vatalanib), may enhance the anticancer potential of the mentioned inhibitors, creating a synergy to inhibit VEGF.

The flavonoid may show one of its anticancer effects by activating FOXO1 and 3 (Forkhead box transcription factor), the gene and transcription factors which induce apoptosis through the upregulation

of other apoptotic genes like Bim and PUMA (Bumke-Vogt et al. 2014; Shukla et al. 2013). Therefore, the flavonoid may enhance the anticancer effect of the FOXO3 activators; metformin, doxorubicin, nipradilol, timolol, melatonin, withaferin A, bortezomib, vorinostat, tunicamycin, paclitaxel, geldanamycin, AZD5363, cisplatin and 5-aza-2-deoxycytidine. Since there is no study which demonstrates the effect of the flavonoid in Hedgehog (Hh) signaling, the signaling which transmits information to embryonic cells for the cell development and survival, until its effect on the signaling becomes clear, it may be reasonable to avoid the apigenin rich foods during the treatments with Hh inhibitors; SANT1-SANT4, CUR-61414, HhAntag-691, GDC-0449, guggulsterone, Saridegib, phthaladines, itracanozole, NVP-LDE225, JAK-441, XL-139, HTS piperidines, MRT-92, MRT-83, PF-04449913, N-acylethanolamides, 2-acylglycerols and 2-alkylglycerol.

The relation of the flavonoid with the anti-apoptotic proteins: One of the most concerned apoptotic proteins which has long been the focus in cancer treatments, p53, act like the brakes in a car, according to the definition of Vogelstein et al. (2010). The definition seems currently the best one since it also highlights the importance of the p53 mutation. The main function of the gen is being a tumor suppressor. The tumor suppressor, p53, may be assumed a kind of brake from two copies, as one from the father and the other from the mother. Suppression of tumor growth can only be possible as the both coppies are altered. But, when only one copy is stuck to the floor, it makes the car continue to go, other words, cell proliferation continues. This distinction allows 'two-hit' test, indicating that if the both copies are altered in the gene, the gene is a tumor suppressor, but if only one copy is altered, the gene becomes an oncogene. But, the strangest observation in the status of p53 is that one copy is generally altered by a base substitution while the other copy is often completely deleted from the cell. When the both copies are altered, other words, when the gen is a tumor suppressor, it suppresses tumorigenesis that is also proven by some studies (Lim et al. 2010; Zheng et al. 2005 and Liang et al. 2007). The wild type (wt) p53 gene, but not its mutant forms, can retard the growth of the cultured cells when overexpressed (Eliyahu et al. 1989 and Finlay et al. 1989). The suppression by the wt-p53 is due to either in cell proliferation or

inhibition in apoptosis. It is now clearly known that wt-p53 inhibits both the cell cycle under some conditions and promotes apoptosis in others. The crystal structure of p53 core domain binds to DNA to inhibit or stop the cell proliferation but any mutation on the core domain abrogates this binding. In many of the tumor suppressions, p53 binds to the cell cycle inhibitor CDK, as in close relation with the downstream regulator of p53, p21/Waf1 to arrest G1 (Brugarolas et al. 1995; Deng et al. 1995) and PUMA (Nakano and Vousden 2001; Yu et al. 2001), activating these pro-apoptotic proteins.

The question of the factors and conditions which cause the mutation of the wt-p53, is still an area to be highlighted. But, the only explanations, according to Freed-Pastor and Prives (2012) are; tumors may select for mutation of p53 solely for loss of wt-p53 tumor-suppressive activity, mutants of p53 may lose certain tumor-suppressive functions of wt-p53, while retaining other aspects of normal wt-p53 and finally, the mutant p53 proteins may gain functions that actively promote tumor growth. Briefly, cancer cells exploit mutant p53 while they are wt-p53 null and this detail crucially indicates to the importance of mutant p53 inhibition which also appears as one of the novel anticancer approaches currently.

Histone deacetylases (HDACs) are a class of enzymes that remove acetyl groups from lysine amino acid on a histone, allowing the histones to wrap DNA more tightly. DNA expression is regulated by the acetylation and de-acetylation and de-acetylation is essential to make the structure of DNA stable. The histone deacetylase inhibitors, a class of compounds, interfere with the function of histone deactylases, weakening the structure of DNA, which appears as a novel approach in the anticancer treatments, presently. Accordingly, histone deactylase (HDAC) inhibitors; suberoylanilide hydroxamic acid (SAHA) the only FDA-approved HDAC inhibitor) (Li et al. 2011), panobinostat (Groselj et al. 2013), PCI-24781 (Lopezet al. 2009), luteolin, EGCG (Amin et al. 2010), CP-31398 (Tang et al. 2007), YK-3-237 (Yi et al. 2013), trichostatin A (Sachweh et al. 2013), Chidamide (Wang et al. 2012), LAQ824 (Yamaguchi et al. 2009), sirtinol, salermide (Peck et al. 2010), FR01228 (as in synergy with doxorubicin) (Blagosklonny et al. 2005), 5-aminoimidazole-4-carboxamide-1-β-4-ribofuranoside (AICAR) (Sengupta et al. 2007), NSC59984 (Zhang et al. 2015), tubacin (Ozaki

et al. 2013) and N-2 (Hwang et al. 2012) are the ones, whose inhibitory effects on mutant p53 or mutation of p53, by increasing acetylation and expression of wt-p53 while fixing the location or restoring wt-p53 signaling via p73 activation in mutant-p53-expressing cells, are observed in the studies of the researchers in the paranthesis.

Prima 1 (a wt-p53 reactivator and inducer of massive apoptosis, a small molecule), NSC319726 (N-[(Z)-pyridin-2-yl)ethyidene]amino] azetidine-1-carbothioamide), stima-1, a low molecular weight compound (specifically to the DNA binding domain of p53), zinc, phikan 083 (a carbazole derivative which is capable of binding with the surface cavity, formed by the mutation that destabilizes p53), CP-31398 (a styrylquinazoline), PK7088 (1-methyl-4-phenyl-3-1H-pyrazole) and maleimide analogs (e.g.MIRA-1, maleimide-derived molecule) may have stronger anticancer potential if they are administered during anticancer diet, rich in zinc (e.g. oyster, beef meat, crab, lobster, yogurt, chese, chicken meat and nuts (USDA 2011), in addition to the apigenin rich foods, since the two bioactive compounds inhibit mutant p53. The mentioned anticancer agents are capable to convert mutant p53 to wt-p53 (Izetti et al. 2014; Yu et al. 2012; Zache et al. 2008; Demma et al. 2010; Puca et al. 2011; Rauf et al. 2013; Takimoto et al. 2002; Liu et al. 2013; Bykov et al. 2005). On the other hand, integrins, namely; integrin β4, increases the adhesiveness of mutant p53 and promotes cancer (Lee et al. 2015). But, integrin inhibitors, namely; RGD peptide (GRGDNP) and fibronectin inhibitors (e.g.anti-integrin; α5β1 antibodies) (Buerkle et al. 2002; Fogerty et al. 1990) decreases the adhesiveness of mutant p53. So, a novel approach at this point, may be the follow-up of an anticancer diet rich in apigenin during the administration of such integrin inhibitors, since apigenin, by inhibiting the mutant p53 and integrin inhibitor, by inhibiting the adhesiveness of the mutant p53, may form a synergy, improving the anticancer potential of the anti-integrin treatments.

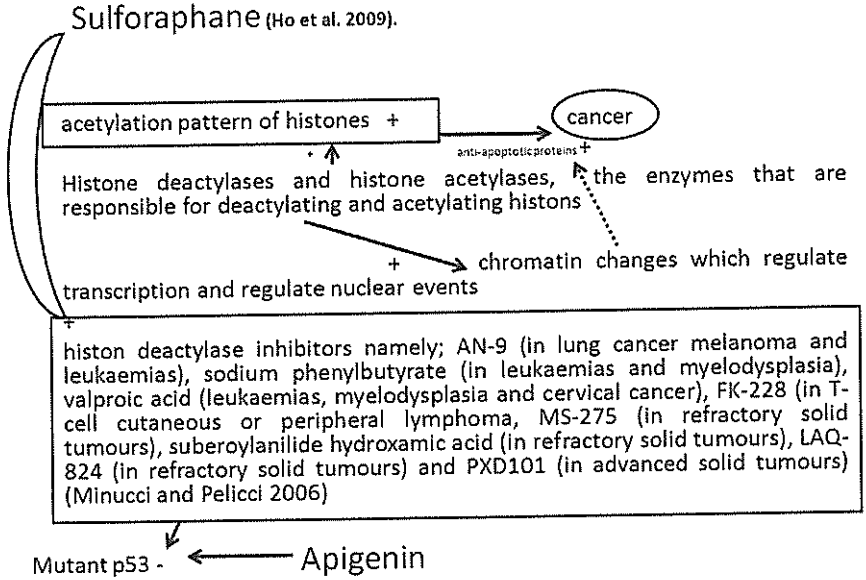


FIGURE 47

Accelerated cholesterol and lipid metabolism are the hallmarks of cancer since cancer cells depend on high insensity of endogenous cholesterol biosynthesis and uptake of lipid particles to build new membranes and maintain active signaling (Gabitova et al. 2013). The important detail here is the activation of the sterol biosynthesis by mutant p53, which may be inhibited by HMG-CoA Reductase inhibitors, commonly known as statitns (Freed-Pastor et al. 2012). This detail may indicate for another important and possible synergy that administers statins in cancer during an anticancer diet rich in apigenin. The 'apigenin and saponin' combination may inhibit mutant p53 while suppressing the sterol synthesis, induced by the gen, and this may increase the rate of inhibition on cell proliferation.

Spautin-1 is one of the inhibitor of autophagy which is a catabolic process through the turnover of proteins, a cellular homeostasis amd mitigation of metabolic stress, either as in pathogenic character or as a response to a disease, like cancer. The molecule acts very specifically in mammalian cells while promoting the degradation of the complex of Vps34 PI3 kinase (a phosphoinositide-3-kinase, involved in cell growth,

proliferation and survival) and beclin 1, the protein which programmes autophagy and tumorogenesis and autophagy-mediated degradation of mutant p53 (Liu et al. 2011). So, treatments which use spautin-1 or any other autophagy inhibitor may benefit from apigenin via a synergy to enhance the degradation level on mutant p53.

STUDIES about the ASSOCIATON of APIGENIN with VAROUS CANCER TYPES

- 160 colon and rectal cancer/2000-2003/alcohol adjusted, smoking adjusted/74-77 years of age/ 10 mg apigenin supplementation (3.5, 3-4.75, 95% CI) versus no apigenin supplementation (R:1.00, 95% CI) reduced the recurrence rate of colon neoplasia in patients with resected colon cancer (Hoensch et al. 2008)/ Cohort.
- 1183 control/1141 ovarian cancer/52-61 years of age/1992-2003/ alcohol adjusted, smoking adjusted/the highest quartile of the flavonoid intake(27.5 mg/d)(1.06, 0.78-1.45, 95% CI) versus the lowest (6.0 mg/d) (R:1.00, 95% CI) decreased the risk (Gates et al. 2009)/Cohort.

EGCG

The most popular beverage, tea, has currently been consumed by two-thirds of the world's population while it contributes to cancer protection with its polyphenols (Chen et al. 2011). All the types of tea, grean tea, black tea and oolong tea, derive from *Camelia sinensis* plant. The differences among the types is that green tea does not readily undergo fermentation while others are totally or partially fermented.

The major components and anticancer agents of the plant are catechins which contain a benzopyran skeleton with a phenyl group substituted at the 2-position and a hydroxyl (or ester) function at the 3-position. The catechins are belong to the flavon-3-ol class of flavonoids while the most abundant catechins in the plant leaves are; (-)-epigallocatechin-3-gallate[(-)-EGCG], (-)-epigallocatechin[(-)-EGC], (-)-epicatechin-3-gallate[(-)-ECG], (-)-epicatechin[(-)-EC], (-)-catechin-3-gallate[(-)-CG], and (-)-gallocatechin-3-gallate[(-)-GCG](Chen et al. 2011). Some of the most common anticancer effects of the green tea catechin, epigallocatechin-3-gallate (EGCG) are; the alteration in the expression of cell cycle regulatory proteins, activation of killer caspases, suppression of oncogenic transcription factors and pluripotency maintain factords (Singh et al. 2011).

EGCG induces the activity of caspase-8 (Das et al. 2010; Tang et al. 2012, Chen et al. 2000; Gupta et al. 2004) which cleaves BID, the protein, situated in extrinsic apoptotic signaling between death receptors and mitochondria which acts as inductor of permeabilization of the outer mitochondrial membrane, releasing cytochrome c and forming apoptosome which activates proteolyze DNA and -3, -7 and -2, all of which proteolyze DNA, and lead to the programmed cell death, apoptosis. Therefore, involvement of tea, especially green one, because of its higher EGCG concentrations, into the anticancer diet, may enhance the anticancer potential of the anticancer drugs; gemcitabine, CP690550 (Tang et al. 2012), costunolide, cisplatin, mitomycin C, garcinol, brefeldin A, valinomycin, piceatannol, kinetin roboside, lipase inhibitor, THL, imiquimod, SC 560, romidepsin, ouabain, digoxin, proscillaridin

A, borrelidin, sanguinarine, bortezomib, MT-21, olinodamine, K858, saikosaponin A, CIL-102 and prodigiosin, since the flavonoid and the anticancer drugs may form a synergy to activate caspases. It should be noted that, curcumin rich foods/plants; e.g. *Curcuma longa* and cinnamon should also be included into the anticancer diet since curcumin activates caspases, similar to tea and the mentioned anticxancer drugs.

Green tea polyphenols and EGCG also alter the expression of cell cycle regulatory proteins. They have currently been claimed to activate the tumor suppressor protein, p53 (Thakur et al. 2012; Cordero-Herrera et al. 2013) and thus, envolvement of green tea into the anticancer diet may increase the anticancer effect of nenzodiazepinedione (BDA), MI-219, MI-63, MI-43, HL-198, CDB3, p53-binding protein 2, CP-31398, p21WAF1/Cip1, nutlins, 37AA, JJ78:12 and KILLER/DR5, since these anticancer drugs activate p53, similar to EGCG of green tea. The addition of beta carotene rich foods; e.g. carrot, amaranth, guava, mango, orange, papaya, spinach, tomato, lettuce, cucumber, green chili, red chili, mint and French bean, may also enhance the same anticancer effect of EGCG in green tea and the mentioned anticancer drugs since beta carotene also activates p53 and may enhance the rate of the synergy.

Oncogenic transcription factors can induce cancer by binding and altering the expression of thousands of genes. Therefore, these factors have often been shown to play critical roles in tumorigenesis and especially in the hematological malignancies. They may bind to a specific DNA consensus sequence or may form a complex with other transcription factors. They mediate their action largely through protein-protein interactions rather than enzymatic activities and affected by any drug. For example, Aryl hydrocarbon receptor (AHR), a cytosolic ligand-activated transcription factor, is involved in various signaling pathways such as cell proliferation and differentiation, gene regulation, cell motility and migration, inflammation and cancer (Feng et al. 2013). When AhR is not bound to a ligand, it is present in the cytoplasm as associated with two molecules of hsp90, the chaperon which plays a crucial role in correct folding and functionality of the proteins in cells (Miyata et al. 2013). As the chaperon binds to a ligand, hsp90 (90 kD heat scock protein) is released, then the ligand in AhR binds to the AhR-response element (ARE) and affects the transcription of

the genes of these elements. Briefly, the release of hsp90 activates the genes, the oncoproteins, in ARE, which directly initiates cancer (Trepel et al. 2010). Hsp90 acts as in a close corporation with its other co-chaperones, including Hop, p23, cdc37, aha1 and pp5. Geldanamycin is one of the cancer chemotherapeutic drugs which attenuates the tumor progression by inhibiting Hsp90 (Miyata et al. 2013). Besides, the following researchers in the parentheses found the inhibitory effects of the following anticancer drugs, on the chaperon, Hsp90; geldanamycin, 17-AAG (tanespimycin), 17-DMAG, IPI-493, radicicol, NVP-AUY922, KW-2478, AT13387, BIIB021, PU-H71, SNX-5422, NVP-BEP800, CUDC-305, XL888 (Neckers and Workman 2012), AT13387, imatinib (Smyth et al. 2012), retaspimycin, metformin (Chen et al. 2013), SNX-2112 (Liu et al. 2012), honokiol (Park et al. 2009), vandetanib (Jane et al. 2009), vorinostat (Ramaswamy et al. 2012), novobiocin (an antibiotic with anticancer effect via the inhibition of Hsp90) (Donnelly and Blagg 2008), cisplatin (Donnely and Blagg 2008), ganetespib (Friedland et al. 2014) and 18β-glycyrrhetinic acid (Kao et al. 2010). On the other hand, EGCG is a novel Hsp90 inhibitor (Yin et al. 2009; Moses et al. 2015 and Li et al. 2009). So, the involvement of EGCG as in supplement form or in green tea, may enhance the anticancer effect of the mentioned anticancer drugs since the flavonoid and these anticancer drugs target cancer cells by inhibiting Hsp90. But, it is also vitally important to note that tamoxifen has been determined to activate Hsp90 (Zhao et al. 2010).

Transcription factors (TFs) are crucial molecules which regulate gene programs that are responsible for the cell renewal differentiation and growth (Stolzenburg et al. 2012). But, the aberrant regulation of TF expression is often associated with specific tumor subtypes (Darnell 2002). For example, the expression of the gene, SOX2, is very critical for the maintenance of self-renewal in embryonic stem cells and neural progenitor cells (Rao et al. 2004; Adachi et al. 2010) and the overexpression of the gene was reported in glioblastoma, non-small cell lung cancer, prostate cancer, hepatocellular cancer and breast cancer (Gangemi et al. 2009; Leung et al. 2010; Bae et al. 2010; Xu et al. 2010 and Chen 2008). Another embryonic stem cell-specific transcriptional factor, Nanog, similar to SOX2, was shown to be overexpressed in cancer (Zhang et al. 2013; Shan et al. 2012).

STAT3, a protein which is activated through phosphorylation of tyrosine 705, in response to various cytokines and growth factors, mediating pluripotency; Ezh2 (Enhancer of zeste homolog 2, which is responsible for healthy embryonic development and cell differentiation), Hedgehog, the signaling of selfrenewal and tumorigenicity, TLR4 (the protein to recognize pathogen and activate immune system, p53 (the gene which protects the genome of the cell and thus it is recognized as tumor suppressor gene), Esrrb (estrogen-related receptor beta, which maintains the expression of Nanog and PI3K/Akt, the signaling which can lead to cancer and radiation resistance during radiotherapy) are the upstream regulators of Nanog, which is one of the stemness factors besides Oct4 and Sox2 while it determines cell fate in both embryonic and cancer stem cells and causes cancer in stem cells when activated, under hypoxia (Stuart et al. 2014; Villasante et al. 2011; Sun et al. 2014, Nachida et al. 2009; Abdelalim and Tooyama 2014; Festuccia et al. 2012; Petruzzelli et al. 2014; Wang et al. 2013; Kim et al. 2006). At this point, a different approach for cancer prevention seems to appear via the inhibitory effect of EGCG on Sox2, HIF1α (the transcription factor which contributes to hypoxia mediated tumor angiogenesis), Nanog (Lee et al. 2013), Bcl-2 (the antiapoptotic protein whose damage or overexpression leads to cancer) (Tang et al. 2012), STAT3 (Yang et al. 2014), Ezh2 (Rajendran et al. 2011) and TLR4 (Byun et al. 2010) while EGCG increases p53 transcriptional activity (Thakur et al. 2012)a and Esrrb (when EGCG concentration is $\geq 5x10^{-6}$M) (Kuruto-Niwa et al. 2000).

The inhibition of the Hedgehog signaling, the pathway which transmits information with Hedgehog proteins to embryonic cells, by the flavonoid (Tang et al. 2012; Slusarz et al. 2010; Liu et al. 2014), during the anticancer drugs which target Hedgehog, may be another reason for the anticancer effect of the flavonoid while this may enhance the anticancer potential of Hedgehog inhibitory anticancer drugs; SANT1-SANT4, CUR-61414, HhAntag-691, GDC-0449, saridegib, phthaladines, mukul, guggulsterone, itraconazole, NVP-LDE225, TAK-441, XL-139, HTS piperidines, MRT-92, MRT-83, PF-04449913, N-acylethanolamides, endocannabionids, IPI926, BMS-833923, LEQ506, GANT61, ribotnikinin, HPI1-4, 2-acylglycerols and 2-alkylglycerol, forming a

synergy between the flavonoid and the mentioned anticancer drugs/ agents via the inhibition of Hedgehog.

The difficulty in evaluating of the anticancer and antioxidant status of a food or food ingredient should clearly be indicated while EGCG has been determined to increase ROS and decrease the levels of the important antioxidant, glutathione (GSH) and thus impairing the mitochondrial membrane potential due to its ROS production, as time, dose and H_2O_2 dependent. As a result, the involvement of EGCG supplementation or green tea into the anticancer diet during the treatments with the anticancer drugs; sunitinib, sorafenib, tetrandrine, cisplatin, bortezomib, vorinostat, MG-132, metformin, thapsigargin, tunicamycin, 17AAg, DBeQ, ritonavir, leptomycin B, ritonavir and brefeldin A, may enhance the anticancer potential of the mentioned anticancer drugs since the flavonoid and the mentioned anticancer drugs target cancer cells by inducing ROS, H_2O_2 and impairing the mitochondrial potential with ROS and H_2O_2, creating a synergy.

Cyclooxygenase (COX), the enzyme whose inhibition can provide relief from inflammation and cancer while its inflammatory product prostaglandin E2 which is often associated with the progress of colorectal cancer (Greenhough ey al. 2009), has been found to be inhibited by the flavonoid (Peng et al. 2006; Kundu et al. 2003; Shimizu et al. 2005; Heinecke et al. 2010; Ownby 2014). So, sunitinib, celecoxib, magnolol, honokiol, eugenol, bis-eugenol, tetrandrine, 17AAG, raloxifene, rofecoxib, nafroxen, dexamethasone, hydrocortisone, triamcinolone acetonide, methyl prednisolone and beclomethasone diproprionate, may have more anticancer effect if they are administered during an anticancer diet which includes green tea or EGCG supplement since the flavonoid and the mentioned anticancer drugs may create a synergy via the inhibition of COX-2 and hence, may form a relief from inflammation during cancer and cancer treatments. On the other hand, the anticancer drugs which have often a side effect by inducing the expression of COX-2; vorinostat, trichostatin A, thapsigargin, okadaic acid, calcium inophore A23187, brefeldin A, tunicamycin, fulvestrant, R(+)-methanandamide, anandamide tetrahydrocannabinol, 12-O-tetradecanoylphorbol-13-acetate (TPA), versipelostatin, lactocystin and MG-132, may show side effect less if they are administered during an anticancer diet which

includes EGCG supplements or green tea. Other words, EGCG may relief and decrease the severity of the side effect due to COX-2 induced by the mentioned anticancer drugs.

One crucial point which should be concerned during the treatments with the anticancer drugs that target cancer cells by inhibiting hem oxygenase-1 (HO-1), the enzyme which produces teratogens, e. g. carbone monoxide, biliverdin and free iron, the anticancer drugs/agents; tin (IV) protoporphyrin 1 dichloride (SnPP), zinc (II) protoporphrin IX (ZnPP), zinc (II) deuteroporphyrin IX-2, 4 bisethyleneglycol, imidazole-based compounds (8, 9,10R,10S,11,12,13,3), caveolin-1, calcineurin, siRNA, metformin, tin-mesoporphyrin, zinc mesoporphyrin (ZnMP), PEG-ZnPP (pegylated zinc protoporphyrin) and OB-24, may be contraindicated with EGCG since EGCG induces the expression of HO-1 (Pullikotil et al. 2012; Zhu et al. 2014).

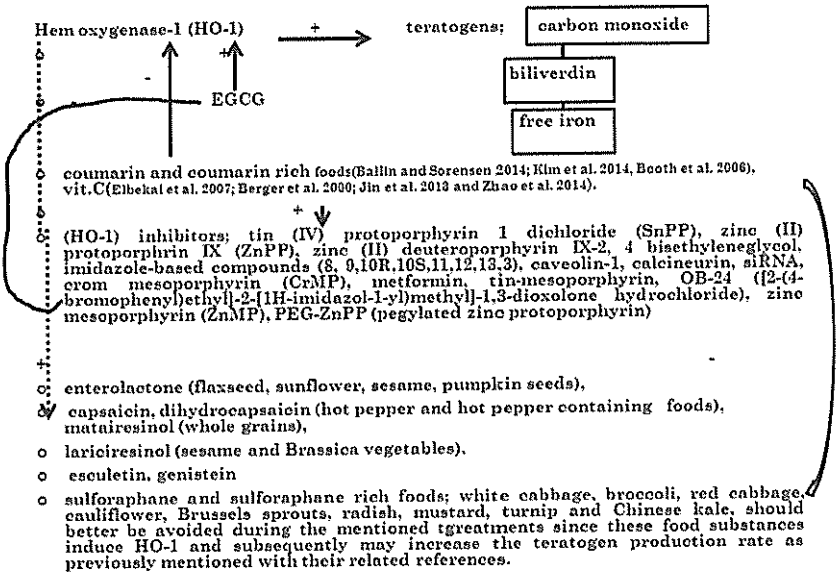


FIGURE 48

Another important point about the flavonoid is that, EGCG was found to suppress the damage to mitochondria induced by ionizing radiation via upregulation of SOD2 (superoxide dismutase 2, the

enzyme which transforms toxic superoxide into hydrogen peroxide and diatomic oxygen and hence, clears up mitochondrial ROS) (Zhu et al. 2014). But, because of the conflicted findings of Oliva et al. (2011), it may be useful not to include green tea and EGCG into the anticancer diet prior to the radiotherapy because of the ambiguity about the effect of the flavonoid on SOD2. Similarly, the enzyme, p38 which induces apoptosis (as being depended on the stimuli and cellular context) by decreasing the expression of cyclin D, was informed to be suppressed by the flavonoid (Chang et al. 2013), but a previous study, carried out by Adachi et al. (2009) reported the opposite. Thus, the effects of the flavonoid on either SOD2 or p38 needs further studies to clarify them.

EGCG also shows anticancer potential by inhibiting the signaling of ERK, the anti-apoptotic protein (serine/threonine kinase) (Tang et al. 2015).

The FOXO forkhead transcription factors FOXO4, FOXO3a and FOXO1a are often associated with their control on cell cycle (Schmidt et al. 2002). These factors are involved in multiple signaling pathways while they regulate the induction of phosphorylation, acetylation/ deacetylation, ubiquitination and protein-protein interactions playing a pivotal role in cell fate decision. They are actively involved in promoting apoptosis as mitochondria dependent and independent by inducing apoptotic proteins; e.g. Fas ligand, TNF, Bim (Bcl-2-interacting mediator of cell death), bnIP3 (Bcl-2/adenovirus E1B 19-kD interacting protein and Bcl-XL (B cell lymphoma XL) (Fu and Tindall 2008). Therefore, their downregulation often appears as an important contributor to the progress of cancer (Prasad et al. 2014). PI3K (Phoshatidylinositol 3-kinase) and Akt (protein kinase B, a serine/threonine-specific protein kinase) are activated by upstream signaling of tyrosine kinases and other receptor molecules through PI3K/Akt signaling (Vivanco and Sawyers 2002) whose aberrant activation has widely been implicated in cancer. The overexpression or the overactivation of FOXO factors induce an apoptotic effect by being able to antagonize the anti-apoptotic PI3K, Akt and PI3K/Akt signaling (Schmidt et al. 2002). On the other hand, EGCG activates FOXO3a (Belguise et al. 2007) and inhibits PI3K/Akt pathway (Shankar et al. 2008). Therefore, the anticancer effects of the anticancer drugs which kill cancer cells by inhibiting Akt, namely; LY29002,

SF-1126, NVP-BEZ235, XL147, XL765, ISC,4, GSK690693, MK-2206, fusedpyrimides, PIP3, GDC,0941, celecoxib, UCN-01, BX,912, BX-320, CCT128930, GDC-0068, perifosine, AT13148, PF-04691502, A47867 and triciribine, may be enhanced with both the anticancer diet containing green tea and/or EGCG since the flavonoid and the metioned anticancer drugs inhibit anti-apoptotic protein, Akt, and hence may form a synergy in creating an anticancer effect. Similarly, since EGCG induces FOXO3, the anticancer drugs which induces the transcription factor; metformin, doxorubicin, nipradilol, timolol, melatonin, withaferin A, bortezomib, vorinostat, tunicamycin, paclitaxel, geldanamycin, cisplatin, AZD5363 and 5-aza-2-deoxycytidine, may have a stronger anticancer effect if green tea or EGCG is included into the anticancer diet because of their synergy to induce FOXO3.

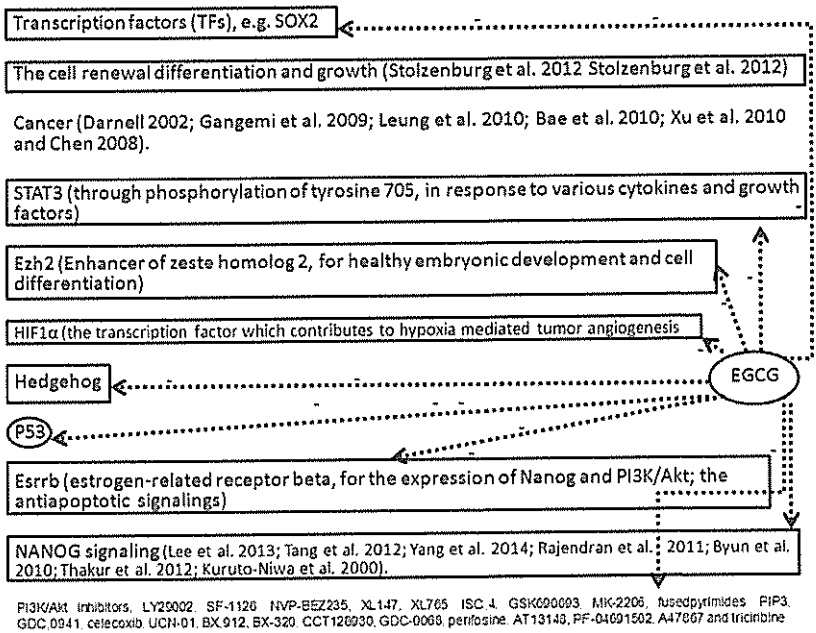


FIGURE 49

The role of the flavonoid on ERalpha, the receptor which is overexpressed in breast cancer and does not respond to endocrine therapy (Ali and Coombes 2000), is not clear with the present

conflicted findings. Li et al. (2010) claims that the green tea polyphenol reactivates ERalpha while Belguise et al. (2007) informs that EGCG reduces ERalpha expression as a result of the inhibition of FOXO3 by the polyphenol. Either the very restricted number of studies or their conflicted results indicates to the necessity of new studies to highlight the effect of EGCG on ERalpha and its status on breast cancer.

That inhibition of the androgen receptor (AR) whose function is the binding to specific DNA sequences and thus controlling the rate of genetic information from DNA to messenger RNA, is another anticancer effect of the flavonoid (Siddiqui et al. 2011; Ren et al. 2000). Similarly, EGCG (50μM) downregulates the acetylation of the receptor and its translocation to nucleus from the cytoplasm (Lee et al. 2012). The following anticancer drugs whose anticancer effect due to their inhibitory effect on AR (that these effects are confirmed with the references in parantheses); sorafenib (Zengerling et al. 2012), cabozantinib (Nguyen et al. 2013), niclosamide (Lui et al. 2014), geldanamycin (Vanaja et al. 2002), ketoconazole (pay attention for its severe side effects!) (Eil 1992), abiraterone acetate (safer than ketocanazole and more potent) (Attard et al. 2009), cyproterone acetate (CPA), megestrol acetate, metroxyprogesterone acetate (attention for their drawbacks such as hepatotoxicity, impotence and cardiovascular side effects) (Helsen et al. 2014), flutamide (with the side effect, gynecomastia) (Kai and Levenson 2011), nilutamide, 6-amino-2-[2-(4-tert-butyl-phenoxy)-1H-pyrimidine-4-one (DL3) (Lu et al. 2007), enzalutamide (Maeda and Saito 2014), selenite and methylseleninic acid (Husbeck et al. 2006), taxol (Gan et al. 2009), docetaxel, paclitaxel (Kahn et al. 2014), thapsigargin (Vander Griend et al. 2009), silymarin (a flavonoid with antioxidant and anti-inflammatory effects on liver, besides its anticancer and AR-agonist attributes) (Zhu et al. 2001), niclosamide (Liu et al. 2014), 17AAG (Solit et al. 2002), fulvestrant (Bhattacharyya et al. 2006), metformin (Lee et al. 2014, faslodex, toremifene, tamoxifen (Kawashima et al. 2004), cisplatin (Chang et al. 2014), doxorubicin (Rokhlin et al. 2006), honokiol (Hahm et al. 2014), may show greater anticancer potential, if they are administered with an anticancer diet which includes green tea and/or EGCG since EGCG similarly inhibits AR, creating a synergy with the mentioned anticancer drugs.

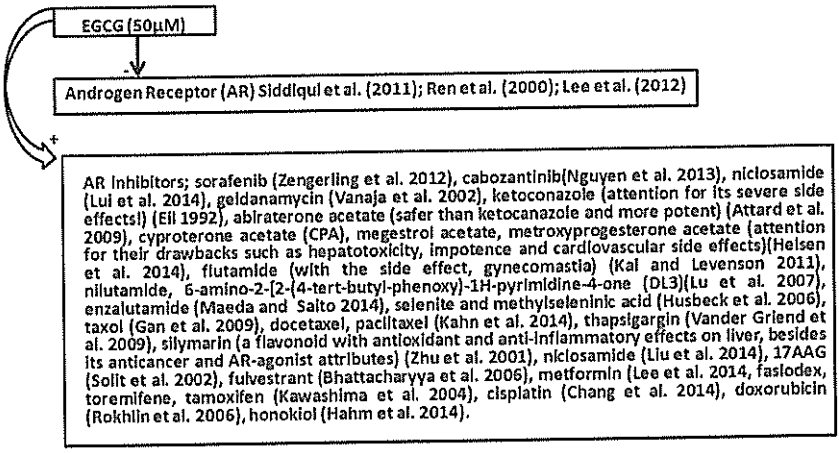


FIGURE 50

The inhibition of metalloproteinases (MMPs), the proteolytic enzymes which contribute to tumor invasion by degrading the surrounding extracellular matrix (ECM), by EGCG as one of the anticancer effects of the flavonoid is confirmed by various studies (Ahmed et al. 2004; Annabi et al. 2002; Sen et al. 2010; Dell'Aica et al. 2002; Hazgui et al. 2008). So, the MMP and collogenase inhibitors; AAG3340, BAY12-9566, CGS27023A, marimastat, bryostatins, lapatinib, BB-94, tamoxifen, radicicol, UO126, metformin, celecoxib, honokiol, 17AAG, raloxifene, tetrandrine, naproxen, ibuprofen, rofecoxib, dxamethasone, bleomycin, hydrocortisone, methylprednisolonone, MG132, vorinostat, tunicamycin, brefeldin A, arfaptin 1, lactacystin and trichostatin A, may have more anticancer potential if they are administered with an anticancer diet which includes EGCG since the flavonoid, like the mentioned anticancer drugs, inhibit MMPs, restricting the invasion of tumor in extracellular matrix.

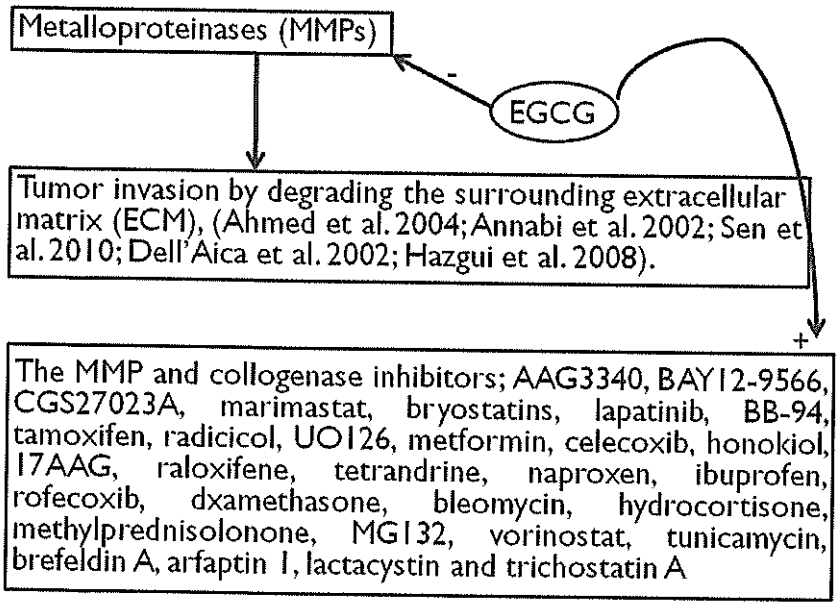


FIGURE 51

TNF which can signall cell proliferation, cell survival via the activation of NF-kB, Ap-1 and Elk-1 (the oncogen proteins), phosphorylation of Erk (tyrosine kinase which activates phosphatidylinositol 3-kinase (PI2K), is inhibited by the flavonoid which may be considered as one of its anticancer effects (Wang et al. 2014; Cao et al. 2013; Riegsecker and Ahmed 2013; Jin et al. 2011). So, the combined administration of TNF and NF-kB inhibitors, e.g. infliximab, etanercept, adalimumab, certolizumab, golimumab, emetine, sunitinib malate, bithionol, narasin, tribromsalan, lestaurtinib, bortezomib, 17-AAG (17-Allylamino-17-Demathoxygeldanamycin), metformin, radicicol, tunicamycin, geldanamycin, ritonavir, honokiol, vorinostat, celecoxib, tetrandrine, naproxen, indomethacin, sulindac, dexamethasone, curcumin, tamoxifen and resveratrol, with green tea and/or EGCG, may enhance the anticancer effect of the mentioned inhibitors because of a possible synergy to inhibit TNF and NF-kB.

The flavonoid also activates the expression of the phase II-antioxidant enzyme, Nrf2 (Na et al. 2008) which may be a contributer

to its anticancer effect. But, it may be vitally important to consider that the flavonoid induces the activation of Nrf2 via the activation of PI3K and Erk which are oncogenic proteins and HO-1 which produces cancerogenic teratogens. Therefore, the induction of Nrf2 by the flavonoid may not mean too much from the point of its inhibitory effect on cancer via the antioxidant, Nrf2, while this induction triggers the teratogenic signaling of PI3K, ERK and HO-1. For this reason, EGCG or green tea, as also previously mentioned, may be contraindicated with HO-1 inhibitors by inducing the Nrf2/HO-1 signaling and thus, may be better avoided during the administration of these anticancer drugs/ agents.

The most crucial point in the evaluation of the anticancer potential of EGCG and its synergy with anticancer drugs is its poor bioavalability. Most of the ingested flavonoid occurs in the small gut but substantial quantities pass from the small to the large intestine where it undergoes further degradation by the local bacterial flora (Lee et al. 2002; Auger et al. 2008).

The peak plasma EGCG concentrations are reached in 1-2 h in the morning and the levels diminish gradually in 24 hours with 3.4±0.3 h elimination half-life (Lee et al. 2002). Besides, the mentioned gastrointestinal inactivation, oxidation due to air contact, Ca^{2+} and Mg^{2+}, sulfation, glucuronidation and the polymorphisms of COMT, the gene whose polymorphisms leads to high neuroticism and low extraversion, decrease the bioavalibility while vitamin C, piperine, fish oil, soft water (high alkali), albumin, fasting and cool and dry storage increases (Mereles and Hunstein 2011). Because of the mentioned poor bioavalibility, EGCG as in supplement form as combined with vitamin C, vitamin C rich foods and/or piperine, may probably show most of its anticancer effect, but EGCG as in the body of green tea, especially as combined with milk and dairy products or green leafy which contain EGCG antagonists; Ca, Mg and S, may have a very restricted anticancer potential and synergy with all the mentioned anticancer drugs above.

Matrix metalloproteinases (MMPs) consist of a multigene family of zinc-dependent extracellular matrix (ECM) endopeptidases whose activity plays a vital role in invasion of tumor growth and metastasis (Gialeli et al. 2011). One of the most commonly known

MMPs, collagenases, are capable of cleaving collagenous extracellular matrix like other MMPs and therefore, they are also crucial in tumor progression and metastasis (Ala-aho and Kahari 2005). So, the MMP and collagenase inhibitors; AG3340, BAY12-9566, CGS27023A, marimastat, bryostatins, lapatinib, BB-94, tamoxifen, radicicol, UO126, metformin, celecoxib, honokiol, 17AAG, raloxifene, tatrandrine, naproxen, ibuprofen, rofecoxib, dexamethasone, bleomycin, hydrocortisone, methylprednisolone, MG132, vorinostat, tunicamycin, brefeldin A, Arfaptin 1, lactacystin and trichostatin A may have more anticancer potential if they are administered with an anticancer diet which includes EGCG

THE STUDIES about the 'EGCG and VARIOUS TYPES of CANCER'

- 50.436 men/404 prostate cancer/1990-2004/alcohol adjusted, smoking adjusted/40-69 years ogf age/≥5 cups/d green tea consumption (0.6, 0.34-1.06, 95% CI) versus <1 cup/d (R:1.00, 95% CI) decreased the risk(Kurahashi et al. 2008).
- 26.481 men/110 prostate cancer/1991-2001/40-79 years of age/ smoking adjusted, alcohol adjusted/≥5 cups/d green tea consumption (0.85, 0.50-1.43, 95% CI) versus <1 cup/d (R:1.00, 95% CI) did not make any change on the risk of prostate cancer (Kikuchi et al. 2006).
- 143 men and women/2002/smoking adjusted, alcohol adjusted/>3 cups/d green tea consumption (0.27, 0.15-0.48, 95% CI) versus < 1 cup/d (R:1.00, 95% CI), decreased the risk of adenocarcinoma (Jian et al. 2004)/case study.
- 5971 men with prostate cancer/smoking adjusted alcohol adjusted/1965-1986/(age adjusted, but not written in the published paper!)/green tea consumption ever (1.47, 0.99-2.19, 95% CI) versus never green tea consumption (R:1.00, 95% CI) had no change (Severson et al. 1989).
- 3400 men/145 prostate cancer/50-84 years of age/1970-1972/ alcohol adjusted, smoking adjusted/>750 ml/d green tea consumption (1.03, 0.58-1.82, 95% CI) versus no green tea consumption (R:1.00, 95% CI) had no effect (Ellison 2000).
- 1390 men/1406 prostate cancer/alcohol adjusted, smoking adjusted/50-74 years of age/≥4 cups/d (1.1, 0.8-1.5, 95% CI) versus no consumption tea (R: 1.00, 95% CI) did not make any change (Villeneuve et al. 1999).
- 69310 women/1255 digestive system(stomach, esophagus, colorectal, liver, pancreas and gallbladder cancers)/smoking adjusted, alcohol adjusted/11 years of follow up/≥3 times/week for >6 months(0.86, 0.74-0.98, 95% CI) versus no green tea

consumption (R:1.00, 95% CI) decreased the risk of colorectal, esophageal and stomach cancer (Nechuta et al. 2012).

- 11907 men and women/108 gastric cancer/1975-1994/46-51 years of age/alcohol adjusted, smoking adjusted/1975-1994/2 cups/d(women:1.3, 0.6-2.6, 95% CI, men: 1.6, 0.9-2.9, 95% CI) did not make any change (Galanis et al. 1998).

AMYGDALIN
The most and the most debated one in the step of anticancer nutrition that we have currently taken, amygdalin:

Leatrile is the simpler semisynthetic version of amygdalin, a cyanogenic glycoside (an agylcone with a cyanide group) which is derived from the aromatic amino acid phenylalanine. These glycosides are stored in the vacuoles in the cells of some plants, e.g. the seeds and wilting leaves of cherry, apple, plum, nonbitter, semibitter and bitter almond, peach, cassava, sorghum, flax, nectarine, apricot, raspberries, cucumber, squash, marrow, giant taro (*Alocasia macrorrhizos*), bamboo (*Bambusa arundinacea Wild*) (Bolarinwa et al.; Femenia et al. 1995; Haque et al. 2002; Serradilla et al. 2016; Mazza and Cottrell 2008).

Amygdalin is a white crystalline, inodorous powder with an intensely bitter taste. The nitrosile is slightly soluble in cold water, alcohol and acetone while it is very soluble in hot water but insoluble in ether (Wang et al. 2015).

Chemically, it is cyanogenic diglucoside with a formula $C_20H_{27}NO_{11}$, with a molecular weight of 457:42 g, a chemical name of D(1) Mandelonetrile-betaglucoside-6beta-D-glucoside (Wang et al. 2012; Song and Xu 2014).

Amygdalin, the aromatic cyanogenic glycoside, can be hydrolyzed into prunasin and mandelonitrile by the glucosidase action of enzymes; such as amygdalase and prunase. The glycoside is ultimately decomposed into benzaldehyde and hydrocyanic acid (HCN) while the later one is the main poisonous substance which needs the mentioned enzymatic activity to form (Suchard et al. 1998). The enzymatic hydrolysis of amygdalin to mandelonitrile forms in acidic condition (pH 5.0-5.8) while the hydrolysis of mandelonitrile to benzaldehyde and HCN proceeds in alkali conditions between ~20-40 °C (Tunçel et al. 1995).

Amygalin; one of the tough & covered debates !!!

Leatrile ⟵ the simpler semisynthetic version of amygdalin, a cyanogenic glycoside (an agylcone with a cyanide group)

Phenylalanine

the seeds and wilting leaves of cherry, apple, plum, nonbitter, semibitter and bitter almond, peach, cassava, sorghum, flax, nectarine, apricot, raspberries, cucumber, squash, marrow, giant taro (*Alocasia macrorrhizos*), bamboo (*Bambusa arundinacea Wild*) (Bolarinwa et al. 2014; Femenia et al. 1995; Haque et al. 2002; Serradilla et al. 2016; Mazza and Cottrell 2008).

FIGURE 52

The inhibition of TNF by suppressing the VEGF induction, as a common anticancer approach, may benefit from amygdalin since amygdalin inhibits the expressions of c-Fos (proto-oncogene), TNF-alpha and IL-1beta (an important mediator of the inflammatory response) (Hwang et al. 2008). The crucial point here is obviously the amount of the cyanogenic glycoside which is toxic and not tolerable above a certain limit. Acute cyanide toxicity can occur between 0.5-3.5 mg/Kg or totally 250 mg in humans (Gosselin et al. 1976; Rasalkar et al. 2010).

The dose of amygdalin for the inhibition of TNF-alpha, c-Fos and IL-beta expressions, Hwang et al. (2008) ≤0.005 mg/Kg seems very safe when compared with the dose, 3.5 mg/Kg which causes acute cyanide toxicity.

Acute cyanide toxicity; **BUT !!!**

0.5-3.5 mg/Kg or totally 250 mg in humans (Gosselin et al. 1976; Rasalkar et al. 2010).

FIGURE 53

The dose of amygdalin which induces the inhibition of TNF-alpha, c-Fos and IL-beta expressions, according to the study of Hwang et al. (2008) is ≤0.005 mg/Kg which seems very safe when compared with the dose, 3.5 mg/Kg which causes acute cyanide toxicity.

Treatment of DU145 (human prostate cancer cells) and LNCaP (human prostate adenocarcinoma cells) with amygdalin which is obtained from *armeniacae* semen by hatching from the shell, making its absorption within the column, concentrating and recrystallizing it with ethanol, induces apoptotic cell death. The apoptotic effect of the glycoside exhibit the anticancer effect by increasing the expression of the pro-apoptotic protein, Bax and caspase 3 enzyme cativity while it decreases the expression of the anti-apoptotic protein, Bcl-2 (Chang et al. 2006). The similar anticancer effect due to the decrease in the expression of Bcl-2 and increase in the expression of Bax by the cyanogenic glycoside (2.5-80 mg/mL was also confirmed by other studies in MDA-MB-231, Hs578T breast cancer cells, HeLa (human cervical cancer cells), COLO201(human colon cancer cells), UMUC-3 RT112 and TCCSUP (bladder cancer cells), H1299 and PA (non small cells lung carcinoma (Lee and Moon 2016; Mantena et al. 2006; Chen et al. 2013; Song and Xu 2014; Makarevic et al. 2014; Qian et al. 2015).

One crucial inspection about the antiangiogenic effect of amygdalin is the decrease in the amounts of microtubules and microvessels of the intraperitoneally injected (3 mg/Kg) amygdalin in rats which clearly indicates to the inhibition of VEGF and subsequently angiogenesis by the glycoside (Mirmiranpour et al. 2012).

One of the anticancer effects of amygdalin is the inhibition on COX-2, the enzyme which is responsible for the production of the inflammatory cytokines and iNOS while iNOS (inducible nitric oxide synthase) is not completely understood due to its dual character in cancer. The molecule can increase the expression of p53, p21 and the activity of caspases that results in G1 arrest, diminishing phosphor Akt, Cdk, RICTOR, the protein as Rapamycin-Insensitive Companion of mammalian Target of Rapamycin, the mammalian target of rapamycin complex 2 (mTORC2) that regulates cell growth and proliferation (Shiota et al. 2006) and cyclin

components, all of which are cell cycle regulating proteins and DNA repair. On the other hand, the same molecule causes the adhesion of molecules, vascular permeability, invasiveness, mutagenesis, oncogene activation and transformation which leads to proliferation (Lechner et al. 2005). But, when the significant anticancer effect of high dose arginine/NO (≥400 μM) and in contrast, the cancerogenic effect of the low dose arginine/NO (<400 μM) are concerned, it it may not be wrong to suggest that amygdalin may protect from the cancerogenic effect of low-dose arginine/NO treatments and/or nutrition which is poor in arginine. Confirmingly, amygdalin (1.25-10 mg/mL), like the high-dose arginine/NO((≥400 μM), diminish phosphor Akt, cdk and cyclin components (the cell cycle regulating proteins), arresting G1 while leading to DNA repair (Makarevic et al. 2014). The cyanogenic glycoside analogues (Dhurrin and Prunasin, 10^{-4}-10^{-10} M%) can reduce the inflammatory cytokines; IL-6, IL-8, IL-23 which are in close relation with tumor progress while it inhibits Hsp70, the antiapoptotic chaperon and the signal activator of IL-6, STAT3 (Paoletti et al. 2013). Amygdalin's one other anticancer effect may be the activation of the pro-apoptotic molecule, p38 mitogen activated protein kinases (p38 MAPK) by the glycoside (Lee and Moon 2016). When all the findings about the mentioned anticancer effects of the glycoside above, amygdalin may be useful as combined with the suppressors of the anti-apoptotic proteins; Bcl-2 and Bcl-xL; namely; HA14-1, AT-101, obatoclax, ABT-263, ABT-737, sunitinib, sorafenib, thapsigargin, bortezomib, 17-AAG, vorinostat, honokiol, metformin, tetrandrine, tamoxifen, geldanamycin, radicicol and raloxifen since the glycoside and the mentoned inhibitors may form a synergy via the inhibition of Bcl-2 and Bcl-xL, triggering apoptosis.

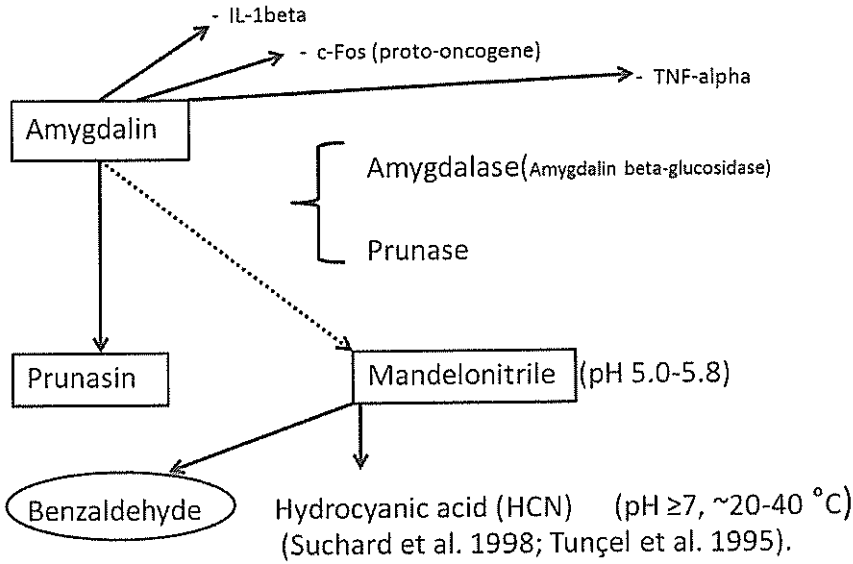


FIGURE 54

The inhibition of VEGF by amygdalin may similarly enhance the anticancer effects of the VEGF inhibitors; sunitinib, sorafenib, bortezomib and MP0250 combination, MG132, MG262, KF58333, 17AAG, geldanamycin, SNX-2112, honokiol, thapsigargin, bafilomycin A1, budesonide, brefeldin A, monensin, ritonavir, bevacizumab, ranibizumab, fulvestra and vandetanib combination, tamoxifen, clomiphene, nafoxidine, ICI182,780, metformin, paclitaxel, tunicamycin and PTK787/ZK222584 (vatalanib), by forming a synergy against angiogenesis via the inhibition of VEGF.

The mentioned inhibitory effect of the glycoside on the inflammatory cytokine, COX-2 and iNOS (the cancer promoting enzyme) may increase the anticancer potential of the iNOS inhibitors; L-arginine, L-canavanine, L-NAMA, L-NNA, N6, NG-dimethyl-L-arginine, L-NIL, NILT, L-NIO, vinyl-L-NIO, AMT, L-thiocitrulline, S-methyl-LL-thiocitruliine, N-propyl-L-arginine, 1400W, A-guanidinoglutaric acid, S-(2-aminoethyl) isothiourea, EIT hydrobromide, mercaptoethylguanidine, S-ethylisothiourea, 1,3-PBIT[1,3-S, S-1,4-phenylenebis(1,2-ethanediyl) bis-isothiourea],1,4-PBIT, aminoguanidine,2-imino-4-methylpiperidine,

RIM (1-[2-trifluoromethyl (phenyl)], imidazole, 7-nitroindazole, 3-bromo-7-nitroindazole and BYK 191023 dihydrochloride (2-(4-methoxy-2-pyridinyl]ethyl]-1H-imisazol [4,5b]pyridine dihydrochloride) and COX-2 inhibitors; sunitinib, celecoxib, magnolo, honokiol, eugenol, bis-eugenol, tetrandrine, 17AAG, raloxifene, rofecoxib, nafroxen, dexamethasone, hydrocortisone, triamcinolone acetonide, methyl prednisolone and beclomethasone diproprionate.

Under the highlight of the inducing effect of amygdalin on caspase activity which is mentioned above, the anticancer drugs that increase caspase activity and subsequently cause ROS influx, namely; costunolide, mitomycin c, garcinol, valinomycin, piceatannol, kinetin riboside, lipase inhibitor, THL (tetrahydrolipstatin), imiquimod, SC560, romidepsin, ouabain, digoxin, proscillaridin A, borrelidin, sanguinarine, MT-21, ionidamine, K858, saikosaponin A, CIL-102 and prodigiosin, may have stronger anticancer effect if the treatments with the mentioned drugs are combined with amygdalin, increasing the activity og caspase enzymes.

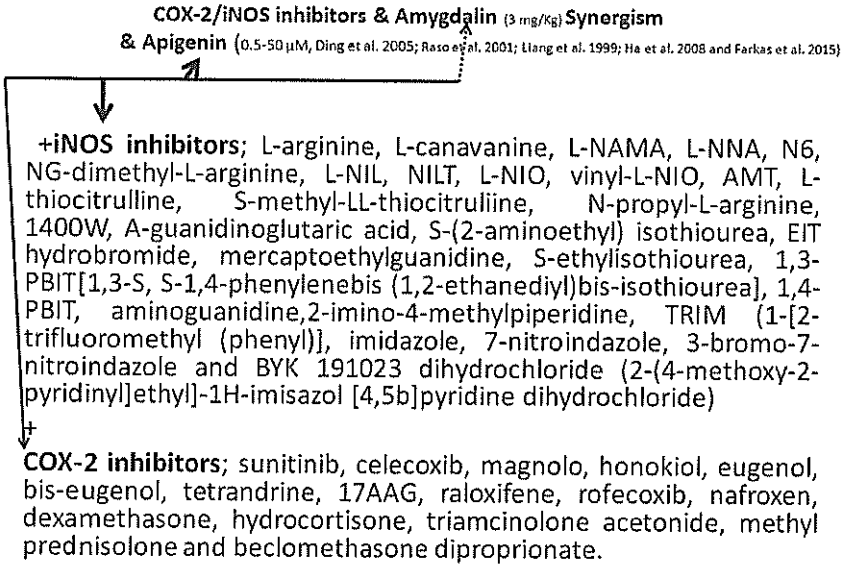


FIGURE 55

Actinomycin D (Jiao and Zheng 2011), Apicidin (Park et al. 2008),

gossypol (a natural yellow pigment derived from the cotton plant, genus *Gossypium*) (Lei et al. 2006); AT-101 (Li et al. 2014), BAM 7 (Gavathiotis et al. 2012), C75, cerulenin (Zeng et al. 2008), paclitaxel (Nonaka et al. 2006), bufalin (a cardiotonic steroid origin ally isolated from the Chinese toas venom) (Sun et al. 2009), CHM1 (Chou et al. 2009), curcumin (Yu et al. 2011), cyclophosphamide (Asiri 2010), gambogic acid (Xu et al. 2009), kamepferol (Marfe et al. 2009), mitomycin-c (Crowston et al. 2002), oxaliplatin (Hayward et al. 2004; Gourdier et al. 2004), 2-methoxyestradiol (Min et al. 2012), 2-indolinones (a series of methylene-bridged heterocycles) (Andreani et al. 2012), piperlongumine (the major effective alkaloid of long pepper plants, C17H19NO5) (Xiong et al. 2015), plumbagin (Qiu et al. 2013), streptozotocin (Koh 2007), TW-37 (Al-Katib et al. 2009), quercetin (Cheng et al. 2010), apigenin (Lu et al. 2010), beta-carotene (Palozza et al. 2004), genistein (Lian et al. 1999), diallyl sulfide (DAS, Allium vegetables, garlic compounds) (Martin 2006), lycopene (Soares et al. 2014), I3C (Rahmen et al. 2000), arginine (Hsieh et al. 2011) and sulforaphane (Gamet-Payrastre et al. 2000), may show greater anticancer potential if they are administered as combined with amygdalin since amygdalin can also induce Bax (Chen et al. 2013; Chang et al. 2006) like the mentioned anticancer agents and bio-active compounds, creating a synergy via the induction of pro-apoptotic Bax effect if the foods rich in these abio-active compounds are consumed as combined with the foods rich in amygdalin, since amygdalin and the menttioned bio-active compounds inhibit IL-1β, creating a synergy which results in the inhibition of inflammation. This approach may improve the potential of the anticancer treatments by inhibiting inflammation during cancer. The mentioned antiinflammatory effect of amygdalin and other bio-active compounds can also hinder the progress of cancer when that some of the proto-oncogenes are produced from inflammatory reactions is considered. On the other hand, resveratrol (Gogada et al. 2011), ascorbic acid (Harakeh et al. 2007), staurosporine, Bci1 and Bci2 (Hetz et al. 2005), all of whose Bax inhibitory effects are determined by the authors in the parantheses, may be contraindicated with the previously mentioned Bax inducing anticancer drugs.and bio-active compounds.

Caspase/ROS/Bax activators & Amygdalin Synergism

Caspase & Ros activators: Costunolide, mitomycin c, garcinol, valinomycin, piceatannol, kinetin riboside, lipase inhibitor, THL (tetrahydrolipstatin), imiquimod, SC560, romidepsin, ouabain, digoxin, proscillaridin A, borrelidin, sanguinarine, MT-21, ionidamine, K858, saikosaponin A, CIL-102 and prodigiosin

Bax activators: Actinomycin D (Jiao and Zheng 2011), Apicidin (Park et al. 2008), gossypol (a natural yellow pigment derived from the cotton plant, genus *Gossypium*) (Lei et al. 2006); AT-101 (Li et al. 2014), BAM 7 (Gavathiotis et al. 2012), C75, cerulenin (Zeng et al. 2008), paclitaxel (Nonaka et al. 2006), bufalin (a cardiotonic steroid origin ally isolated from the Chinese toas venom) (Sun et al. 2009), CHM1 (Chou et al. 2009), curcumin (Yu et al. 2011), cyclophosphamide (Asiri 2010), *gambogic acid* (Xu et al. 2009), kamepferol (Marfe et al. 2009), mitomycin-c (Crowston et al. 2002), oxaliplatin (Hayward et al. 2004; Gourdier et al. 2004), 2-methoxyestradiol (Min et al. 2012), 2-indolinones (a series of methylene-bridged heterocycles)(Andreani et al. 2012), piperlongumine (the major effective alkaloid of long pepper plants, $C_{17}H_{19}NO_5$) (Xiong et al. 2015), plumbagin (Qiu et al. 2013), streptozotocin (Koh 2007), TW-37 (Al-Katib et al. 2009), quercetin (Cheng et al. 2010), apigenin (Lu et al. 2010), beta-carotene (Palozza et al. 2004), genistein (Lian et al. 1999), *diallyl sulfide* (DAS, *Allium* vegetables, garlic compounds) (Martin 2006), lycopene (Soares et al. 2014), I3C (Rahmen et al. 2000), arginine (Hsieh et al. 2011) and sulforaphane (Gamet-Payrastre et al. 2000).

FIGURE 56

Under the highlight of the inducing effects of the bio-active compounds; quercetin, apigenin, beta-carotene, genistein, kaempferol, curcumin, lycopene, arginine, I3C, sulforapahane and amygdalin, briefly, the following foods/plants; caper, onion, cocoa powder, cranberries, cherries, green tea, black tea, lettuce, asparagus, green pepper, tomatoe, apple, broccoli, cauliflower, bok choy, mango, watermelon, white cabbage, red cabbage, radish, mustard, turnip, Chinese kale, beans, endive, kale, blueberries, cherry, parsley, plum, apricot, capsicum pepper, *Gingko biloba*, *Talia* spp., *Equisetum* spp., *Moringa oleifera*, *Sophora japonica*, propolis, tuna, salmon, avacado, green peas, Mustard greens, crab, arthicoke, garlic, guava, chamamolie, wheat sprout, grapefruit, *Curcuma longa*, cinnamon, fava bean, kudzu, lupine, psorolea, miso, amaranth, cucumber, mint, green chili, red chili, lupin, mollusk, lentil, sesame seed, soy flour and chickpea, may be advised as a detailed diet, consisting of the mentioned foods and herbs which are rich in the mentioned bio-active compounds, during the treatments with the Bax inducing anticancer drugs, creating a synergy to form apoptosis via the induction of Bax. The diet with its bio-active compounds that induce Bax may be crucially important by increasing the apoptotic effect of the anticancerdrugs which target Bax induction since Bax permeabilizes the outer mitochondrial membrane, triggers

the release of apoptotic proteins like cytochrome c while inducing ROS influx which results in the activation of apoptotic caspases (Hsu et al. 1997; Antonsson et al. 2001; Li et al. 1997), the induction of Bax has appeared as one of the current and novel approaches in anticancer treatments.

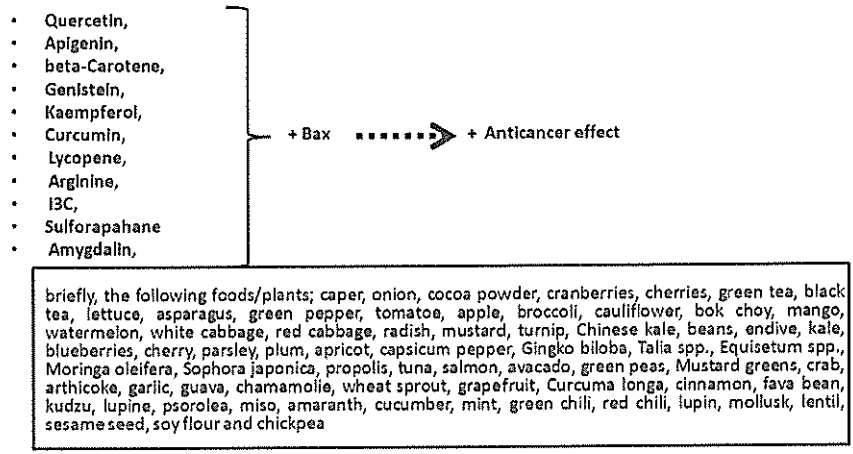


FIGURE 57

The extracellular signal-regulated kinase (ERK) signaling pathway is one of the major determinants in the control of cell proliferation, survival and differentiation (Kohno and Pouyssegur 2006). These properties may be linked to temporal differences in the strenght and location of ERK within the cell (Yoon and Seger 2006). Different expression levels and phosphorylation of early gene products are induced by ERK signaling, like Fos (a proto-oncogene and a 380 amino acid protein with a basic leucine zipper region which means a secondary three-dimensional structure in a protein) whose expression is induced by stimuli, serum, growth factors, cytokines and UV radiation and Jun, a component of the transcription factor activator protein 1 (AP-1) which binds and activates AP-1 to transcript oncoproteins (Vleugel et al. 2006; Murphy et al. 2002). On the other hand, the intramuscular injection of amygdalin (0.005 mg/Kg) which can signal for the cell proliferation and IL-1beta (the cytokine as the mediator of inflammatory responses)

but also the expression of c-Fos (Hwang et al. 2008). Accordingly, the c-Fos inhibitory effect of amygdalin may improve the anticancer effect of T-5224 whose c-Fos inhibitory effect is determined by Miyazaki et al. (2012).

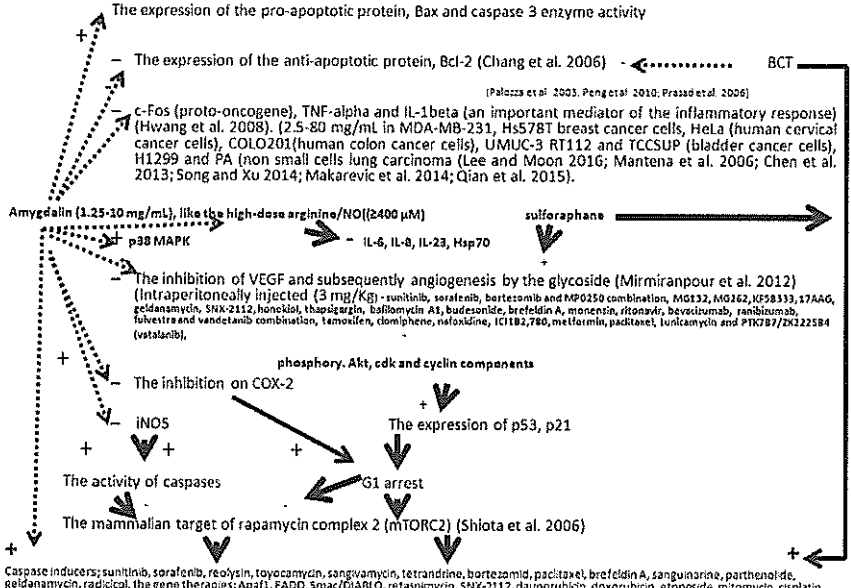


FIGURE 58

Although resveratrol seems to be contraindicated with the anticancer drugs and amygdalin which inhibit Bax, resveratrol inhibits IL-1 beta, like amygdalin and thus, a diet rich in both bio-active compounds, containing; peanuts, grapes, blueberries, cherry, apple, plum, bitter almond, peach, flax, nectarine, *Alocasia macrorrhizos* and *Bambusa arundinacea* wild, may be advised, in particular with its inflammatory IL-1 beta inhibition during cancer. Other bio-active compounds which inhibit IL-1beta; sulforaphane (Choi et al. 2014), arginine (Meldrum et al. 1997), I3C (Jiang et al. 2013), kaempferol (Kowalski et al. 2005), EGCG (Singh et al. 2002), quercetin (Yoon et al. 2011), apigenin (Zhang et al. 2014), genistein (Kim et al. 2014), resveratrol (Shakibaei et al. 2007), ascorbic acid (Candelario-Jalil et al. 2006), beta carotene (Bai et al. 2005) and lycopene (Hung et al. 2008), may have stronger antiinflammatory

effect if the foods rich in these bio-active compounds are consumed as combined with the foods rich in amygdalin, since amygalin and the mentioned bio-active compounds inhibit IL-1β, creating a synergy which results in the inhibition of inflammation. This approach may improve the potential of the anticancer treatments by inhibiting inflammation during cancer. The mentioned antiinflammatory effect of amygdalin and other bio-active compounds can also hinder the progress of cancer when that some of proto-oncogenes are produced from inflammatory reactions is considered. On the other hand, the inhibitory effects of Fos which are currently used currently in Oncology, may be enhanced if they are combined with amygdalin rich foods or amygdalin supplementation because of the previously mentioned inhibitory effect of amygdalin on c-Fos, creating a synergy with the Fos inhibitors whose c-Fos inhibitory effects are approven by the studies of the authors in parenthesis. Although the inhibitory effects of both amygdalin and the mentioned anticancer agents and bio-active compounds on c-Fos are currently highlighted, the effects of I3C, quercetin and folate are still waiting to be highlighted. Therefore; if the approach in anti-cancer treatment is the use of Fos inhibitors; a diet containing fesitin rich foods, namely; strawberry (whose fesitin concentration is 160 μg/g), apple (26.9 μg/g), persimmon (10.6 μg/g), lotus root (5.8 μg/g), grape (3.9 μg/g), kiwi (2.0 μg/g), peach (0.6 μg/g) (Kimira et al. 1998), genistein rich foods/ plants; soy bean, fava bean, kudzu, lupine, psoralea, miso, apigenin rich foods/plants; grapefruit, artichoke, Chinese cabbage, bell pepper, garlic, celery, guava, kaempferol rich foods/plants; broccoli, endive, tomato, blueberries,, celery, plum, apricot, *Ginkgo biloba*, *Talia* spp., Equisetum spp., Moringa oleifera, *Sophora japonica* and propolis, sulforaphane rich foods; white cabbage, Brussel sprouts, radish, mustard, cauliflower, turnip and Chinese kale, arginine rich foods; turkey breast, beef, ground meat, lupin, soybean, nuts, seeds, egg white, peanut, mollusk, chickpea, soy flour, sesame seed, lentil, beans, chicken meat and porl meat and genipin (Gardenia fruit) may be advisable since all the foods with their bio-active compounds may help for the inhibition of c-Fos, making a synergy with each other and the other agents that inhibit c-Fos. It should be considered carefully that, opposite to the Fos inhibitors, beta-carotene, though it is an important bio-active compound which has got

a significant anticancer potential as reviewed in detail in its related part, may induce proliferation and so, may have a tumor promoting effect when used in 3 and 10 μM (Dulin ska et al. 2005) by inducing the expression of c-Fos. On the other hand, it seems too early to make an evaluation about the cancer promoting effect of the pro-vitamin since only the low doses (3-10 μM) have been proven to induce cell proliferation while the higher doses are anti-proliferative. The detailed mechanism of this unexpected effect of the pro-vitamin in lower doses still remains covered. Like the lower doses of beta-carotene, the doses to which can be easily reached in smokers!, another bio-active compound to induce c-Fos expression is resveratrol when it is 100 μM (Wolter et al. 2003) as similar to radicicol (Ki et al. 2000).

Amygdalin can destroy trophoblasts, the cells which form the outer layer of a blastocyst (a structure and inner cell mass which forms the embryo). According to the theory of Griffin (1997), pancreas destroys the trophoblasts followed by the embryo formation, otherwise, trophoblasts would circulate through the body of both mother and infant, making them vulnerable to cancer (Griffin 1997). The trophoblasts, though they are the formers of the embryo, if not destroyed by the chymotrypsin enzyme of pancreas, just after embryo formation, do exhibit the characteristics of cancer, spreading and multiplying rapidly into the uterus wall where the embryo can attach itself for maternal protection and nutrition. The theory is also in parallel with a very old theory of Beard which claims as a defensive reaction of derepressed genes in the aberrant germ cells or somatic cells against intramural parasitization by trophoblast, leading to hyperplasia in primitive somatic cells (Gurchot 1975). One of the most important key points of both theories is that, cancer arises from trophoblasts that escape from the destruction of pancreatic enzyme, chymotrypsin and form the derepressed aberrant germs and somatic cells which begin to dominate in cancer as a response to previously mentioned intramural parasitization by trophoblasts (Ross 2015). Both of the thesis underline the same cornerstones in the initiation of cancer. In the case of pregnancy, trophoblasts are triggered to form placenta and umbilical cord by the effect of hormone, estrogen, which is present in both males and females. But, in other cases, the trophoblasts may be triggered as a part of a healing process as in a response to a wide range

of carcinogens which have long been studied, from allergens, nutrient compounds, toxic minerals to microorganisms like yeast, fungus, bacteria and virus. The latter may be regarded as a healing process which is not terminated upon completion of its task (Day 1999) which results in cancer. On the other hand, Human Chorionic Gonadotropin (hCG) is the hormone which is produced by the embryo following implantation (the very early stage of pregnancy at which the embro adheres to the wall of uterus) (Cole 2009). The pituitary analog of hCG is known as luteinizing hormone (LH) which is produced in the pituitary gland of both males and females of all ages (Hoermann et al. 1990). hCG is mainly used for detection and monitoring of pregnancy but it is also very sensitive and a specific marker for trophoblastic tumours of placental, germ cell origin and testicular germ cell tumors. Elevated serum levels are observed in 45-60 % of patients with biliary and pancreatic cancer and in 10-30 % of most other cancers (Stenman et al. 2004) while it is significantly higher in serum of 67 % of patients with malignant ovarian tumours (Lenhard et al. 2012). That there is no study to highlight a detailed association between amygdalin and trophoblast is a painfull missing in the field of cancer treatment and nutrition that it will continue to cause cancer patients to ask the very expensive and time consuming biopsy process while the serum hCG levels which could easily be detected in urine might be a valuable indicator for cancer, not only in non pregnant women but also men. But, this question continues to be exist since it has been informed as a theory by Krebs in 1950 (Krebs and Beard 1950). Non-pregnant women and men have only very small amounts of hCG, with blood levels less than 5 mLIU/mL. Higher levels may indicate cancer (Germa-Lluch et al. 1980; Szturmowicz et al. 1995), though it may yield a poor prognosis in some cancers. One more question among many others about amygdalin, waiting to be answered is the effect of amygdalin on trophoblasts and hCG levels. If the theory of Krebs is correct (that we still continue not to know because of the lack of studies about the association of amygdalin with trophoblasts and hCG), if the stem cells or at least many cancers are trophoblasts in which even a very few of them may serve as a precursor for tumour formation, can amygdalin destroy these trophoblasts and subsequently decrease the levels of hCG, without giving a severe damage to healthy cells in lung

cancer since lung cancer cells and though not definitely known but with a high probability other cancerous cells, have lower rhodanese activity?. Can the same probability of the anticancer potential of amygdalin work for the other cancer types if they have lower rhodanese activity like lung cancer cells?. Answering all these questions can only be possible with the urgently needed studies which target the effect of amygdalin on trophoblasts, hCG as compared with the healthy cells, in terms of toxicity.

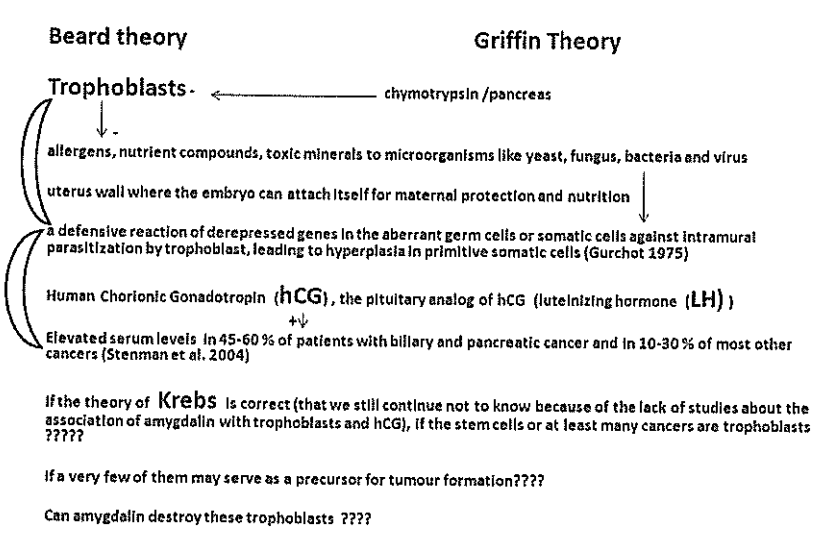


FIGURE 59

The only study in literature about the association of amygdalin and trophoblast is a very old review of Greenberg (1980) refutes the anticancer potential of amygdalin by considering many causative agents of cancer like viruses, heredity, physical and chemical agents while the author evaluates trophoblasts as only a minor causative factor of a minor range of cancer types, the cancers of only female and male reproductive system, like chorioepithelioma. But, the review is too far from giving any plausible finding or answer for the possible inducing effects of these carcinogenic agents (e.g.heredity, viruses ect..) on trophoblasts

with the same reason, lack of studies to analyse 'the cancerogen agent and trophoblast' association. The acidification of tumors by cyanide in amygdalin was also claimed as ineffective since the disruption of lysosomes in cancer cells requires an acidity of pH 6 or less, an acidity level which is not possible to reach, according to the author. But, it may be possible that, the direct intravenous injections of amygdalin to tumor area may increase the acidity level of the media where cancer is exist. Similarly, in spite of the author's claim without any finding and evidence, there is still no study to highlight the possible acidity increase by amygdalin in tumors. If amygdalin does not have any effect enough to raise the acidity which can only be answered with new studies, then an acidic solution of amygdalin and its administration into the cancer area may be a new approach which may worth to be tried.

Nonetheless, one of these very few studies administered 3 g amygdalin (as intravenous) which is higher than the toxic limit '1 g/d' and did not find any improvement in symptoms but cyanide toxicity (Moertei et al. 1982). Syrigos et al. (1998) conjugated beta-glucosidase, the enzyme which catalyzes the hydrolysis of the glycosidic bonds to terminal non-reducing residues in beta-D-glucosides and oligosaccharides, with release of glucose while the enzyme activity was determined as the highest in Caco-2, followed by HT29 and T84 cell lines, all of which are colorectal adenocarcinoma cells (Arafa 2009). Although it is the only study about the association of beta-glucuronidase and cancer, the study of Kim and Jin (2001) determined beta-glucuronidase activity as 1.7 times higher in colon cancer cells than healthy cells which may indicate to a possible higher activity of beta-glucosidase, the enzyme which belongs to the same family with beta-glucuronidase. The question here is the possibility of higher vulnerability of cancer cells to amygdalin if they have higher beta-glucosidase activity than healthy cells. Under this occasion, such a higher beta-glucosidase activity in cancer cells may release more cyanide and benzaldehyde from glucose in these cancer cells and this may lead to a less amygdalin toxicity on healthy cells. The answer lies in researches which are urgently required to show the activity level of beta-glucosidase in different types of cancer cells but currently there is no study, analyzing the association of the enzyme activity and cancer cell, as compared with the healthy cells.

Beta-glucosidase activity will uncover the Amygdalin dilemma

- beta-glucuronidase activity 1.7 times higher in colon cancer cells than healthy cells (Kim and Jin, 2001) which may indicate to a possible higher activity of beta-glucosidase, the enzyme which belongs to the same family with beta-glucuronidase.
- Such a higher beta-glucosidase activity in cancer cells
- release of more cyanide and benzaldehyde from glucose in these cancer cells
- less amygdalin toxicity on healthy cells.
- **The question here is the possibility of higher vulnerability of cancer cells to amygdalin if they have higher beta-glucosidase activity than healthy cells???!!!**

FIGURE 60

In spite of the mentioned risk of amygdalin toxicity which remains cloudy because there is no data about the compared beta-glucosidase activities in different cancer cells and healthy cells, the study of Syrigos et al. (1998) may be a cornerstone, since the authors conjugated the enzyme to a tumour-associated monoclonal antibody (a bladder cancer associated) with amygdalin to activate amygdalin specifically at the tumor site, without any systemic toxicity usually associated with chemotherapy. This approach, described by the authors as 'antibody-directed enzyme prodrug therapy (ADEPT)' could have been modified and improved for many other cancer types, but the study of Syrigos et al. (1998) has remained the only one of its kind. However, the conjugation of specific monoclonal antibody to a particular type of cancer as combined with amygdalin and beta-glucosidase may gain amygdalin a novel anti-cancer agent potential without any systemic toxicity.

The study of Syrigos et al. (1998) may be a cornerstone, monoclonal antibody (a bladder cancer associated) + amygdalin (without any systemic toxicity usually associated with chemotherapy!!!).

'antibody-directed enzyme prodrug therapy (ADEPT)' can be modified and improved

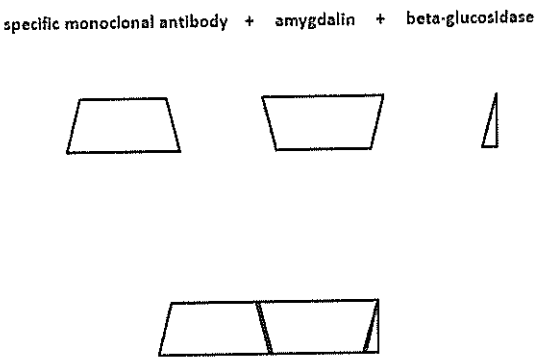


FIGURE 61

There is an important amount of data from in vitro studies and a few of cohort studies which targeted 'amygdalin and cancer' association. Amygdalin (1.25-10 mg/mL) was shown to inhibit UMUC-3, RT112 (human bladder cancer) and TCCSUP (urinary bladder cancer cell line) (Makarevic et al. 2014), RCC (renal cancer cell line) (Juengel et al. 2015), SNU-C4 (human colon cancer cells) (Park et al. 2005). Laster and Schabel (1975), Wodinsky and Swiniarski (1975) observed increase in life span of amygdalin treated animal groups. Stock et al. (1978b) observed 22% lung metastasis in amygdalin (1000 mg/Kg/d) treated mice while it was 91 % in nontreated ones. Biaglow and Durand (1978), Lea and Koch (1979), Alfrey et al. (1977), Kwon et al. (2003), Li et al. (2015) (who followed the approach of Syrigos et al. (1998), 'antibody-directed enzyme prodrug therapy (ADEPT)' and Navarro (1959), were the other scientists who observed a significant anti-tumor activity or an increase in life-span of patients. But, Ovejera et al. (1978) did not observe any inhibitory effect on breast and colon cancer tumor cells. Additionally Hill et al. (1976), Stock et al. (1978a) and Chitnis et al. (1985)

did observe significant increases in apoptosis levels while Koeffler et al. (1980) did not observe any selective inhibition of myelogenous leukemia cells, liver cancer cells and lymphocytic leukemia cells.

Amygdalin contains four substances. Two of them are glucose, the third is benzaldehyde and the fourth is cyanide. Cyanide and benzaldehyde are poisons if they are in free form and not bound within other molecules to amygdalin. Vitamin B_{12} is very close in structure and contains cyanide but it is not harmful because the cyanide is bound with another molecule. Sulfur in the enzyme, rhodanese whose isozymes are exist in humans (Whitehouse et al. 1988) binds cyanide of amygdalin to thiosulfate in the enzyme and converts it into thiocyanate (Cipollone et al. 2008). Blood thiocyanate is mainly distributed in serum and its presence is regarded as evidence of cyanide detoxification. Thiocyanate has 1% the toxicity of cyanide and it is readily eliminated by the kidneys while smoking, renal failure, respiratory disease and cardiovascular disease are the main predisposed factors which may cause to higher cyanide and thiocyanate blood levels. Moreover, thiocyanate which is taken orally is completely absorbed by the body, with a distribution volume; 0.25 L/ Kg and 3 day half-life (Cailleux et al. 1988) while thiocyanate toxicity does not present a serious problem even in intravenous infusion of sodium nitroprusside (one of the main anaesthetics which is converted into thiocyanate by rhodanase) (Schulz 1984). The cyanide in amygdalin which is delivered to the cells by glucose is neutralized by rhodanese but the activity of the enzyme is different in cancer and healthy cells. For example, the activity of the enzyme is significantly lower in lung cancer cells than healthy one, claimed by Jamshidzadeh et al. (2001) while their study is the only study which compares the enzyme activity in normal and cancer cells.

Questions and Questions

If the cyanide and the benzaldehyde which are transferred by the means of amygdalin to the cells are neutralized by rhodanese and if the activity of the enzyme is proven to be lower in cancer cells than healthy cells, this means the higher tendency of the cancer cells to cyanide than healthy cells. This detail may appear a significant and important novel approach in cancer treatments. The mentioned lower activity of rhodanese in lung cancer cells may indicate to a possible and important anticancer potential of amygdalin as a novel anticancer agent in lung cancer. It is very obscure to understand the reason why there is still no study about the compared activities of rhodanese in different types of cancer cells and healthy cells. Only after the activity of the enzyme in different cancer cells as compared with the healthy ones is determined, then amygdalin toxicity for the particular cancer cell which has got lower rhodanese activity than the healthy ones, may have been exploited in favor of the healthy cells since the healthy cells with their higher rhodanese activity will be much more resist to the amygdalin toxicity while the particular cancer cells will not, like in lung cancer cells. Yet, there is no study (except the one belongs to Jamshidzadeh et al. 2001) about the enzyme activity of different cancer cells as compared with healthy cells. Why there is still no study to exploit the amygdalin toxicity against lung cancer cells and others if the only study of Jamshidzadeh et al. (2001) has already indicated to the lower rhodanase activity in lung cancer cells than the normal healthy cells?. If the lower activities of the enzyme in various cancers are determined, amygdalin may be injected into those cancer cells with target therapies as combined with or without rhodanese injections and may exhibit a strong potential to shrink tumours. Similarly, the other question which is still waiting to be answered is; the association of amygdalin and its inhibitory effect on trophoblasts. It should be noted that, it is a high possibility if amygdalin is tried tıo be injected as combined with rhodanese since the enzyme may neutralize it and thus may decrease its effect. Under this circumstance, rhodanese may

be injected long after amygdalin shows its anticancer effect. But, these possibilities like others remain to be questions due to the lack of studies.

The nutshell about the amygdalin's effect on cancer is that it may have an important anticancer potential and may be a novel and promising anticancer agent, especially when applied with 'antibody-directed enzyme prodrug therapy (ADEPT)' which eliminates amygdalin's toxicity (which has long been targeted and criticized). Although, there is an important amount of in vitro and in vivo studies which claim its ineffective role on some cancers, a great number of in vitro and cohort studies indicate to its possible anticancer potential. Under the highlight of all these studies and their findings and especially the novel amygdalin treatment 'ADEPT', it is not scientifically correct to define amygdalin's role on cancer as quackery, or at least, the time for such a definition is too early!. Moreover, it remains obscure not to reach any literature with blocked web pages when it comes to amygdalin, though we can currently reach either correct or quackery data of many other food substances and bio-active compounds!!!.

The STUDIES about AMYGDALIN and it's ASSOCIATION with CANCER

One of the most crucial and vital missing points about the currently most debated bio-active compound is the lack of any cohort which search for the anticancerogen effect of amygdalin by comparing the long term/high dose and long term/low dose administrations. In spite of the many mentioned in-vitro and in-vivo studies which clearly highlight and make indication to the various anticancerogenic effects of amygdalin. Ironically, the compound which is currently in the center of hot debates, has still got no any cohort! Except the one which is mentioned below;

- 29133 men/876 lung cancer/50-69 years of age/ alcohol adjusted, smoking adjusted / 6.1 years of follow up / 20 mg beta carotene supplementation (0.10-0.29, 0.17, 95% CI) versus no supplementation (R:1.00, 95% CI) reduced the risk (The Alpha-Tocopherol Beta Carotene Cancer Prevention Study Group, 1994).

Glucose, Fructose and Cancer Dilemma:

Increased glucose flux and metabolism induce cancer via the proliferation, anti-apoptotic signaling, cell cycle progression and angiogenesis while cancer cells become more addicted to aerobic glycolysis (Koppenol et al. 2011), since they need glucose for ATP production for their proliferation. The tendency of malignant cells to glucose which results in their apoptosis when they face with the lack of glucose has also been confirmed (Shim et al. 1998). Opposite, diabetogenic glucose concentrations, 11 mM, as compared to 5.5 mM, leads altered expression of genes which promotes cell proliferation in breast, colon, prostate and baldder cancer (Masur et al. 2011). Confirming these findings, the reduction of plasma glucose levels and calorie restriction, significantly prolong the survival in tumor-bearing animals (Santisteban et al.; Seyfried et al. 2003). Finally, hyperglycemia has clearly become a predictor of poor survival in patients with various cancers (Derr et al. 2009; Weiser et al. 2004; McGirt et al. 2008; Krone and Ely 2005; Jee et al. 2005; Ikeda et al. 2009; Stattin et al. 2007). According to Gatenby and Gillies (2005), the upregulated and aerobic glycolysis may be an adaptation to intermittent hypoxia in pre-malignant lesions with a microenvironmental acidosis which leads to acid-resistant cancerogen cells. But, all these findings which have gained a perfectly high acceptability in literature and media run and hit against the wall, because the several fast-growing cells overexpress the P2X7 receptor (P2X7R, P2X purinoceptor 7), which upregulates the glucose transporter Glut1, the glycolytic enzymes, glyceraldehydes 3-phosphate dehydrogenase (G3PDH), phosphofructokinase (PFK), pyruvate kinase M2 (PKM2) and pyruvate dehydrogenase kinase 1 (PDHK1), while increasing the activity of anti-apoptotic protein pathway, phosphorylated Akt/PKB, and the extension of hypoxia-inducible factor 1α (HIF-1 α), all of which increase glucose and lactate levels required by cancer cells (Amoroso et al. 2012). Briefly, glycose deprivation cannot be accepted to slow or protect cancer progress since cancer cells can adapt themselves to the glucose and fructose deprived microenvironments, by using the receptor, P2X7. It has uppermost

significance that glucose, fructose and calorie restrictions and avoidance of their high consumptions may be crucial to gain a protection against cardio-vascular diseases, hypertension, diabet, cancer and many other metabolic diseases and disorders. But, the findings of Amoroso et al. (2012) clearly indicate that glucose or fructose which may be produced from glucose during aerobic glycolysis via convertion of glucose-6-phosphate to fructose-6-phosphate (Achcar et al. 2012) should not be concerned as the only culprit in cancer formation and similarly, their deprivations should not be accepted as smart approaches in cancer prevention, especially when the great contents of glucose or fructose in a great amount of foods are concerned. Such approaches concerning glucose or fructose's triggering effect on cancer cells will not have to be meanless since cancer cells will continue to adopt themselves via P2X7, including hypoxia and producing glycose more !, but also the patient with cancer will be required to avoid from legumes, cereals, fruits, animal origin foods, dairy products.., concerning that they contain glycose or fructose which clearly seem ridiculous since such diets and approaches will send the patient directly malnutrition, the collapse of immunity and death, even faster than ever!.

One of the biggest myths in cancer nutrition; fructose feeds and triggers cancer cells as the only culprit and thus, it should be out of the list!!

The pentose phosphate pathway is a metabolic pathway (parallel to glycolysis) that generates NADPH (Nicotinamide Adenin Dinucleotide Phosphate), the cofactor which is used in anabolic reactions, such as lipid and nucleic acid synthesis. The pathway also forms pentoses and ribose 5-phosphate, the precursors for the synthesis of nucleotides. Besides, it involves the oxidation of glucose and acts as anabolic rather than catabolic. In the pathway, glucose-6-phosphate is converted into ribulose-5-phosphate via 6-phosphogluconolactone and 6-phosphogluconate. Then, ribulose-5-phosphate forms ribulose-5-phosphate and ribulose-5-phosphate-3 epimerase which are converted into glyceraldehydes 3 phosphate and sedoheptulose 7-phsophate via ribose-5-phosphate and xylulose-5-phosphate by the action of transketolase. Finally, glyceraldehydes 3-phosphate and sedoheptulose 7 phosphate form fructose 6 phosphate, erythrose 4-phosphate and xylulose-5-phosphate into glycolysis. Briefly, the intake of glucose is going to be ended by fructose formation from glucose. Other words, glucose is the precursor of fructose in metabolism. Therefore, the restriction of fructose in cancer nutrition to be avoided from the risk of cancer is meaningless as long as almost all the foods contain glucose which is converted into fructose, sooner or later, but definitely!. In conclusion, fructose depletion cannot have any significant effect since all foods contain glucose in less or high amounts, glucose as the precursor of fructose. Therefore, the depletion of glucose rather than fructose appears much more effective to deprive cancer cells from nutrients, but such approach can not be logical since it has not any acceptable base in practice when glucose existence in all foods is considered. Thus, the limitation of fructose or fructose rich foods, while there is a great amount of foods with their glucose contents, appears as the first myth in cancer nutrition, currently. Confirming this, cancer cells have been found to suppress glucose uptake by non-tumour

cells in the premetastatic niche by secreting vesicles that carry high levels of the miR-122 microRNA. The cancer-cell-secreted miR-122 triggers metastasis by increasing nutrient availability, especially fatty acid synthesis, for the premetastatic niche while suppressing glucose uptake by healthy cells (Fong et al. 2015).

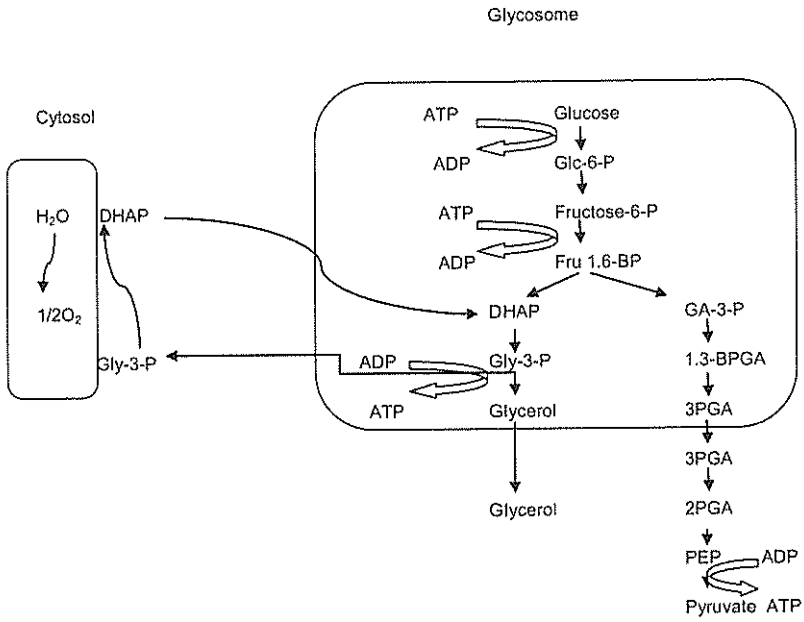


FIGURE 62

Either glucose or fructose, without any discrimination between them, is underlined by the current data indicating to glucose as the precursor of fructose. Glycolysis which generates ATP, is primarily based on glucose and fructose while it is upregulated in cancer cells, results in an increased glucose consumption. This may also be proposed as an adaptation to intermittent hypoxia in pre-malignant lesions. The upregulation of glycolysis leads to microenvironmental acidosis of glycolysis leads to microenvironmental acidosis which requires an evolution to phenotypes resistant to acid-induced cell toxicity. What seems typical for cancer cells which differentiate them from the healthy ones are both of the upregulated glycolysis and subsequently acid

resistance (Gatenby and Gillies 2004). Like the fallacy of considering fructose as the only culprit in cancer formation while neglecting its precursor, glucose, another fallacy is the claim of 'glucose deprivation' as a new cancer therapy which is impossible practice because of glucose existence in almost all foods. But, under the highlight of the findings above, caloric restriction with the limitation in glucose, fructose and lipid rich foods, may be adviced as much more rational preventive measure in cancer nutrition. Glucose, fructose and lipid in such a vicious circle, generate oxygen radicals, which attribute to oncogenic mutations, while activated oncogenes and loss of tumor suppressors, in turn induce aerobic glycolysis (the Warburg effect in which cancer cells predominantly produce energy by a higher rate of glycolysis). Glucose together with glutamine, via glycolysis, provides the carbon skeletons, NADPH (which is essential for nucleic acid and lipid synthesis) and ATP to build new cancer cells which persist in hypoxia, leading to an evolution of cancer cells to high resistance of Warburg effect (Dang 2012). In fact, the nonsense of the discrimination between glucose and fructose and the necessity to realize the equal potential of both glucose and fructose, was recognized more than 30 years ago. Reitzer et al. (1979) claimed that galactose or fructose are preferentially shunted into glycolytic subsidiary pathways but they do not generate substantial amounts of glycolytic ATP, a capability which allows cancer cells to proliferate in absence of glucose. This early claim in the history of cancer nutrition also indicates to the equal cancerogen potentials of glucose, fructose or galactose and nullity of proposing fructose as the only culprit of cancer in the current media and literature!. While glucose or fructose may shunt into glycolytic subsidiary pathways in the absence of glucose and vice versa, glucose may enter into the pathway in the absence of galactose or fructose!!!!. On the other hand, cancerous cells and several fast-growing cells overexpress the P2X7 (purinoreceptor 7), a protein that is encoded by the P2X7 gene in humans for extracellular ATP. These P2X7 receptor expressing cells upregulate the glucose transporter Glut1, the glycolytic enzymes; glyceraldehydes 3-phosphate dehydrogenase (G3PDH), phosphofructokinase (PFK), pyruvate kinase M2 (PKM2) and pyruvate dehydrogenase 1 (PDHK1). Furthermore, the expression of the same receptor inhibits pyruvate dehydrogenase (PDH) activity,

increases phosphorylated Akt/PKB and finally hypoxia-inducible factor 1α (HIF-1 α) expression, all of which lead to the proliferation of cancer cells while enhancing the glycogen stores (Amoroso et al. 2012).

Although glutamine is a nonessential amino acid, cancer cells display addiction to it since glutamine plays an essential role in the uptake of essential amino acids and in maintaining activation of TOR kinase, the protein to activate translation of proteins in order to cell growth and proliferation by manufacturing more proteins. Moreover, the non essential amino acid is the primary mitochondrial substrate and is required to maintain mitochondrial membrane potential and integrity while it supports NADPH production which is needed for redox control, lipid and nucleic acid synthesis (Wise and Thompson 2010). PKC-zeta (PKCζ), the enzyme which plays an important role in insulin-stimulated glucose transport, has also been emerged as a crucial compound which makes glutamine more responsible for cancer more responsible than glucose or fructose. PKCζ free cancer cells cannot utilize glucose or fructose but such cells are more capable in using alternative carbon sources like glutamine. Therefore, the glucose and fructose depletion therapies might only work against tumors as long as the cancer cells are producing PKCζ. Otherwise, these cells are able to use alternative nutrients, especially glutamine. Moreover, the lower the PKCζ, the more the aggressive the tumor is. Confirmingly, Ma et al. (2013) showed that PKCζ deficiency promotes the plasticity, necessary for cancer cells to reprogram their metabolism to utilize glutamine through the serine biosynthetic pathway in the absence of glucose while the patients with low levels of PKCζ have a much poorer prognosis. At this point, putting all the blame to only fructose appears as an incorrect approach in the current media and literature since the precursor of glutamine is glucose (Hankard et al. 1997), like it is the precursor of fructose.

The meaningless of the approach which targets glucose or fructose deprivation is not only because of a great amount of foods that contain fructose or glucose, but also many of these foods are rich in the anticancer vitamins, minerals and bioactive compounds. Port (fortified wine), sherry (fortified wine), blackcurrant juice, orange and lemon juice, lime fruit juice, orangei apple, celery, pear, pineapple, biscuit, bread (from wheat flour), dried fruit, muffin (from white flour),

breakfast cereal, corn flakes, oat bran, hamburger, beef pattie, fried egg, lettuce, tomato, onion, cheese, jam, mayonnaise, mustard, blackbean, plum, soy and soy products, apricot, banana, blueberry, cherry, date, fig, fruit salad, grape, kiwi, lychee, mandarin, mango, melon, peach, raspberry, strawberry, fish, chicken and lamb meats, honey, syrup (golden), beetroot, cabbage, capsicum (red, raw), carrot, chilli (red, raw), cucumber, eggplant, ginger, parsnip, pumpkin, squash, sweet potato and zucchini are the foods which have more than 1 gram of fructose per 100 gram (archive.foodstandards.gov.au). The main paradox here is that most of the mentioned foods in the list like; carrot, raspberry, strawberry, ginger, pumpkin, sweet potato, onion, celery, apple, orange, pineapple, grape, plum, kiwi, cherry, date, fig, melon, mango, peach and apricot are the foods which are richest in some anticancer vitamins, minerals and bioactive compounds from vitamins C, B, A, E to minerals Se and Zn to bioactive compounds namely; apigenin, quercetin, I3C, amygdalin, genistein, kaempferol, lycopene, sulforaphane and arginine. Most of those bioactive compounds, vitamins and minerals with their food sources are listed in detail in the related parts, as in their relation with the chemotherapeutic agents. The unusual status of these foods in cancer nutrition is that they are rich in both cancerogenic glucose or fructose and anticancer bioactive compounds, vitamins and minerals. What seems very clear is that, an approach to reject all these foods under the pretex of their rich glucose or fructose contents will be useless, meaningless, inadvisable and unpractical since such approach will have to lead the deprivation of a rich content of anticancerogenic bioactive compounds, vitamins and minerals in the same foods as well. No need to mention that, there will be a very few amounts of food to be consumed by the patients with cancer since many of them contain glucose, fructose or galactose. Accordingly, instead of the deprivation of anticancerogenic bioactive compounds, mineral or vitamin rich foods which are also rich in glucose or fructose, the limitations in glutamine rich foods; soy and soy products, turkey meat, chicken meat, chicken broth, crustaceans, seeds, game meat, cheese, fish meat, ostrich, pork meat, spirulina, cabbage, veal meat, beef meat, mollusks, asparagus, milk and broccoli (Nutritiondata.self.com), will appear as another solution which will have to hit the wall like the limitations in fructose

or glucose!. Because, glutamine is required for the activation of TOR kinase, the protein to activate translation of proteins in order to cell growth and proliferation, to maintain mitochondrial membrane potential and integrity and NADPH production which is needed for redox control, lipid and nucleic acid synthesis. This important nonessential amino acid will be deficient in such glucose and fructose limitations, causing the collapse of immunity!. The most intelligent and rational approach may be fish meat, broccoli and asparagus with their higher Omega 3, but lower glutamine contents. Under the highlight of all these findings, it is obvious that it may be a beneficial approach to combine the anticancerogenic drug-like effect of many of the fruit, vegetable, soy and legumee with their rich anticancerogenic bioactive compounds, vitamins and minerals with the limitation in animal origin foods rich in glutamine while restricting the calorie intake (lipids and simple carbohydrates) by consuming fruits and vegetables (especially the cruciferous ones) which are low in calorie with their complex carbohydrates while they are rich in anticancerogenic bioactive compounds, vitamins, minerals. Most of the studies mentioned below show the intelligence of such approach.

- A metaanalysis from 16 studies claim the decrease in risk with the highest quartile of cruciferous vegetable intake (0.78, 0.69-0.99, 95% CI) versus the lowest (R:1.00, 95% CI) for colon cancer, 9 studies claim the highest quartile of cruciferous vegetable intake (0.91, 0.74-1.13, 95% CI) versus the lowest (R:1.00, 95% CI) for rectum cancer / alcohol adjusted, smoking adjusted (Wu et al. 2013).
- 11492 control / 1991-2009 / 1468 oral cavity and pharynx cancer, 505 esophagus cancer, 230 stomach cancer, 2390 colorectum cancer, 185 liver cancer, 326 pancreas cancer, 852 larynx cancer, 3034 breast cancer, 367 endometrium cancer, 1031 ovary cancer, 1294 prostate cancer, 764 kidney cancer / 58-63 years of age / ≥1 portion/d consumption of cruciferous vegetables (0.83, 0.70-0.98, 95% CI) for oral cavity and pharynx cancers, (0.72, 0.52-0.99, 95% CI) for esophagus, (0.90, 0.61-1.30, 95% CI) for stomach, (0.83, 0.74-0.94, 95% CI) for colorectum, (0.72, 0.47-1.11, 95% CI) for liver, (0.90, 0.63-1.30, 95% CI) for pancreas,

(0.84, 0.67-1.05, 95% CI) for larynx, (0.83, 0.74-0.94, 95% CI) for breast, (0.93, 0.68-1.27, 95% CI) for endometrium, (0.91, 0.76-1.11, 95% CI) for ovary, (0.87, 0.70-1.09, 95% CI) for prostate and (0.68, 0.54-0.84, 95% CI) for kidney, decreased the risk of all the mentioned cancer types / alcohol adjusted, smoking adjusted (Bosetti et al. 2012)

- 41.837 postmenopausal women / 4 years of follow-up / 55-69 years of age / green leafy vegetable consumption (≥5 serving / week (0.92, 0.55-1.54, 95% CI) versus ≤1 serving/week (R:1.00, 95 % CI) decreased the risk of lung cancer / alcohol adjusted, smoking adjusted (Steinmetz et al. 1993).
- 1.793.327 men and women / 16 years of follow up / 593 cases of lung cancer / 30-69 years of age / smoking adjusted, alcohol not / the highest quartile of vegetable intake (0.8, 0.6-1.1, 95% CI) versus the lowest quartile (R:2.00, 95% CI) decreased the risk of lung cancer (Speizer et al. 1999).
- 77283 women, 47778 men / 519 lung cancer / 30-75 years of age / 10 years of follow up / smoking adjusted, alcohol adjusted / highest quartile of vegetable intake for women (>7.2 sevings/d) (0.79, 0.59-1.06, 95% CI) versus the lowest quartile (3.4-4.5 servings/d) (0.79, 0.61-1.03, 95% CI) did not make any difference (Ferkanich et al. 2000).
- 22631 men and women />18 years of age / 15 years of follow-up / smoking adjusted, alcohol not / the highest quartile of cruciferous vegetable intake (0.52, 0.29-0.92, 95% CI) for women and (0.72, 0.37-1.37, 95% CI) for men versus the lowest (R:1.00, 95% CI) decreased the incidence rate (Lam et al. 2010).

GENISTEIN

Genistein (4', 5,7-trihydroxyisoflavone) is a small molecule abundantly exist in soy and soy products (Messini et al. 2006). This naturally derived compound is a a member of the flavonoid family of small molecules which includes over 5000 compounds (Veitch and Grayer 2008). Genistein contains several hydroxyl groups (which are responsible for the most of its antioxidant and anti-cancer effects), attached to its 3-phenylchromen-4-one backbone which consists of two benzene rings linked by a heterocyclic pyran rink (Pavese et al. 2010). The richest sources according to the current analytical findings are; soybean, fava bean, kudzu, lupine, psoralea and the fermented soybean product, miso (Kaufman et al. 1997). The isoflavone induces the mitochondrial permeability transition by the generation of reactive oxygen species (ROS) (Salvi et al. 2002). Similarly, according to Sanchez et al. (2008), the flavonoid acts as pro-oxidant and increases the apoptotic effect of anti-leukemic agent arsenic-trioxide (ATO), by activating the down-regulation of BCl-xL (B-cell lymphoma-extra large, a transmembrane molecule in the mitochondria). Bcl-xL prevents the release of mitochondrial contents such as cytochrome c which would lead to caspase activation. So, the down-regulation of the Bcl-2 family protein releases cytochrome c and ROS from the mitochondria and as a result, activates caspase-3 and caspase-8/Bid (the proapoptotic protein from Bcl family) which results in apoptosis.

Though it seems first as conflicted with these findings, Kim et al. (2014) inform that, the flavonoid is an antioxidant which decreases GSH (glutathione, the antioxidant) and GSSG (glutathione disulfite) levels. The decreases in the levels of these antioxidants and also the flavonoid induced down-regulation of the enzymes which are involved in GSH synthesis may also result in ROS accumulation which may lead to apoptosis of cancer cells by these ROS. The same authors even claim that the ROS accumulation in the mitochondria induces transmembrane mitochondrial activity, releasing ROS into the cytoplasm, activating Bid and caspases and hence, sensitizing leukemia cells to ϒ-radiation. These

findings with the previous ones, may be important and useful and may indicate to the necessity to include soybean, favabean, kudzu, lupine, psoralea and miso into the anti-cancer diet, especially in the period before radiotherapy.

According to Lee et al. (2014), the flavonoid increases Nuclear factor (erythroid-derived 2) factor 2 (Nrf2), the factor which mediates oxidant production and increases ROS (KOvac et al. 2015). Under the highlight of these findings, because of the antioxidant effect or opposite, oxidant effect, it clearly seems that there are an influx of ROS from mitochondria into the cytoplasm and subsequently the accumulation of them in the cytoplasm due to the effect of the flavonoid. Therefore, the anti-cancer drugs which target cancer cells by producing ROS, namely; sunitinib, sorafenib, tetrandrine, cisplatin, bortezomib, vorinostat, MG-132, metformin, thapsigargin, tunicamycin, 17AAG, DBeQ, ritonavir and brefeldin A, may have a much stronger anti-cancer effect if they are administered with an anti-cancer diet which includes genistein and/or genistein rich foods like soybean, favabean, kudzu, lupine, psoralea and miso, since all the mentioned anti-cancer drugs and the flavonoid may form a synergy, killing the tumor cells by producing or influxing ROS to these cells.

As being in close relation with ROS production and increase in mitochondrial membrane transition, genistein induces caspases, the Ca^{2+}-dependent proapoptotic proteases, mu-calpain, caspase-12 (Sergeev 2004), caspase 7, signaling kinase 1-p38 mitogen-activated protein kinase (Shim et al. 2007), caspase 3 (Yang et al. 2007), caspase 9 (Dhandayuthapani et al. 2013), caspase 4 (Das et al. 2009), which is one of the initial reason for the apoptotic effect of the flavonoid (Kumi-Diaka and Butler 2000). The caspase inducing effect of the flavonoid may enhance the anti-cancer potential of the anti-cancer drugs which target cancer cells by activating caspases namely; costunolide, cisplatin, mitomycin C, garcinol, brefeldin A, valinomycin, piceatannol, kinetin riboside, lipase inhibitor, THL (tetrahydrolipstatin), imiquimod, SC 560, romidepsin, ouabain, digoxin, proscillaridin A, borrelidin, sanguinarine, bortezomib, MT-21, lonidamine, K858, saikosaponin A, CIL-102 and prodigiosin, by including the genistein rich foods/plants; kudzu, favabean, soybean, lupine, psoralea and miso into the anti-cancer diet.

One important anti-cancer effect of the flavonoid with a different mechanism is via the inhibition of the anti-apoptotic protein, galectin-3 that the flavonoid induces the expression of the tumor suppressor protein, p21, which arrests cell growth in galectin-3-expressing cancer cells while it does not have the same effect on normal cells (Lin et al. 2000).A very limited number of the anti-cancer drugs which bind galectins for today; thiodigalactoside diester bis-[3-O-(3-methoxybenzoyl)-β-D-galactopyranosyl] sulfane (Td131_1) (Lin et al. 2009), OTXOO8, sunitinib (Zucchetti et al. 2013), combined use of paclitaxel and pectasol-c modified citrus pectin (Pect-MCP) (Hossein et al. 2013) and bortezomib (Mirandola et al. 2011), may show more anti-cancer effect if they are administered during genistein supplementation or/and genistein rich foods/plants containing diet (e.g. soybean, favabean, kudzu, lupine, psoralea and miso) since the flavonoid and the mentioned anti-cancer drugs may form a synergy to inhibit galectins.

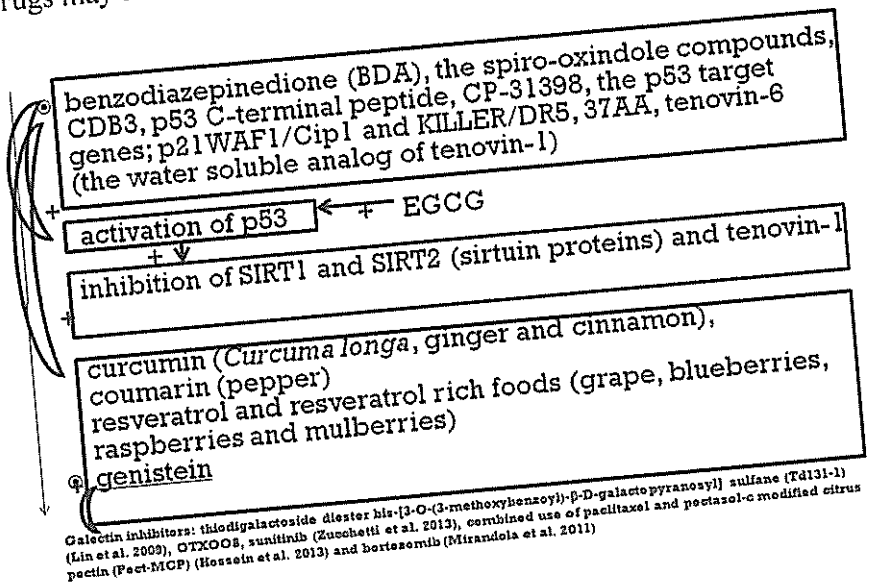


FIGURE 63

The flavonoid inhibits the expression and activity of the enzyme, COX-2 which is responsible for the inflammatory hormone production (Chung et al. 2014; Ye et al. 2004; Swami et al. 2009 and Shon et al. 2006). The inhibitory effect of the flavonoid on COX-2 may enhance

the anti-cancer potential of the anti-cancer drugs; sunitinib, celecoxib, magnolol, honokiol, eugenol, bis-eugenol, tetrandrine, 17AAG, raloxifene, rofecoxib, nafroxen, dexamethasone, hydrocortisone, triamcinolone acetonide, methyl prednisolone and beclomethasone diproprionate, since the mentioned anti-cancer drugs similarly inhibit COX-2 and hence, may form a synergy with the flavonoid. The inhibition of COX-2 due to the synergy between the flavonoid and the anti-cancer drugs, not only enhance the anti-cancer effect but also may improve the relief from the inflammation since COX-2 serves as an enzyme to produce inflammatory hormones.

Genistein's one important effect which may contribute to cancer prevention with a novel mechanism may be the decrease by the flavonoid in IL-6, the cytokine which is involved in inflammation and infection (Relic et al. 2009; Ji et al. 2012). The deregulated overexpression of the multifunctional cytokine and its signal activator, STAT3, is associated with the inhibition of apoptosis, stimulation of angiogenesis and drug resistance and inflammation (Guo et al. 2012; Bromberg and Wang 2009). Confirmingly, IL-6 appears as a key cytokine since its inhibition as combined with or without STAT3 inhibition, especially in colorectal cancer (Waldner et al. 2012), breast cancer (Sun et al. 2014), skin cancer (Lederle et al. 2011), liver cancer (He et al. 2013), brain tumours (Lilja et al. 2001), chronic myelogenous leukemia (Reynaud et al. 2011) and bone metastasis and cancer (Ara and Declerck 2010). The cytokine's induction of inflammation also contributes to the progress of cancer since cancer may stem from inflammation while inflammatory cells and inflammation regulators like IL-6 may facilitate angiogenesis and promote tumor growth (Lu et al. 2006). The following STAT3 inhibitors whose STAT3 inhibitory effects are confirmed by their following authors within parathesis; S3I-201 (Siddiquee et al. 2007), stattic (Schust et al. 2006), STA-21 (Park et al. 2014), WP1066 (Horiguchi et al. 2010), cucurbitacin B (Chan et al. 2010), 5,15-diphenylporphyrin (5,15-DPP) (Uehara et al. 2009), niclosamide (You et al. 2014), auranofin (Kim et al. 2007), galiellalactone (Don-Doncow et al. 2014), kahweol (Kim et al. 2012), cepharanthine (Chen et al. 2012), SD1008 (Duan et al. 2007), nifuroxazide (Nelson et al. 2008), cryptotanshinone (Shin et al. 2009), ruxolitinib phosphate (Shi et al. 2011), STAT3 inhibitor VII (Sun et al. 2015), sunitinib, sorafenib (Yamamoto et

al. 2014), bortezomib, guggulsterone (Li et al. 2009), paclitaxel (Zhang et al. 2015), honokiol (Rajendran et al. 2012), metformin (Vasamsetti et al. 2015), 17-AAG (Fumo et al. 2004), vorinostat, romidepsin (Tiffon et al. 2011), tetrandrine (Ma et al. 2015) and IL-6 inhibitors; tocilizumab (Hennigan and Kavanaugh 2008), sunitinib (Anglesio et al. 2011), sorafenib (Yang et al. 2012), metformin (Zhao et al. 2014), radicicol (Hsiao et al. 2013), 17-AAG (Tsui et al. 2008), monensin, brefeldin A (Schuerwegh et al. 2001), raloxifene (Kasai et al. 2011), bortezomib (Roccaro et al. 2006), siltuximab (Guo et al. 2010), honokiol (Li et al. 2011) and curcumin (Chan et al. 2003) may show greater anti-cancer and anti-inflammatory effect if they are administered with an anti-cancer diet rich in genistein containing foods/plants; e.g. soybean, favabean, kudzu, lupine, psoralea and miso. It may be useful to note that, any anti-cancer drug, in addition to the mentioned ones, which may induce inflammation as side effect, may also benefit from the use of the genistein rich foods and plants in the anti-cancer diet.

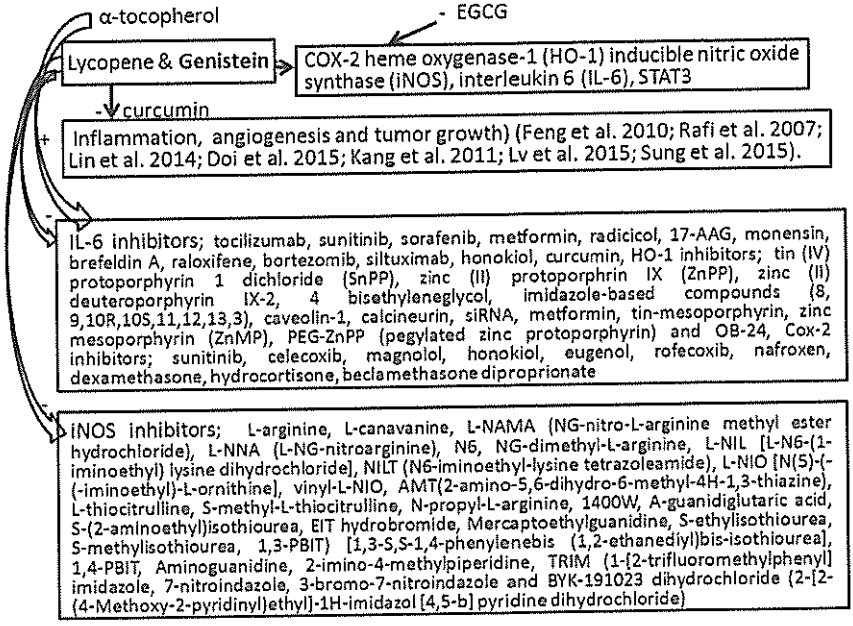


FIGURE 64

The inhibition of GRP78, the central regulator of endoplasmic reticulum (ER) and the chaperon which controls ER with its protein folding capacity by the flavonoid (Hong et al. 2005; Zhou and Lee 1998), may be the other anti-cancer effect of genistein. This inhibition may induce ROS influx into the cytoplasm and subsequently the induction of the apoptotic caspase activity. Therefore, the consumption of genistein rich foods/plants; kudzu, soybean, favabean, lupine, miso and psorolea, may enhance the anti-cancer potential of the anti-cancer drugs which target cancer cells by inhibiting GRP78, namely; sunitinib, sorafenib, SCH727965, metformin and bortezomib combination, tunicamycin, radicicol, KUSs, versipelostatin, pyrivinum pamoate, tanespimycin, 17-AAG or the anti-cancer drugs which target cancer cells by producing ROS and inducing ROS influx, due to the GRP78 inhibition, namely; sunitinib, sorafenib, tetrandine, cisplatin, bortezomid, vorinostat, MG-132, metformin, thapsigargin, tunicamycin, 17AAG, DBeQ, ritonavir and brefeldin A, since the flavonoid, like the mentioned anti-cancer drugs, inhibits GRP78 and as a result, causes ROS influx and caspase activation.

Epidermial Growth Factor (EGF)-induced disassociation of FOXO3, the gene and transcription factor which triggers apoptosis through the upregulation of the apoptotic genes, Bim, PUMA, p53 and p27, is inhibited by the flavonoid, favoring Foxo3-p53 (mutated) interactions with the promoter of the cell cycle inhibitor p27, promoting cell cycle arrest (Qi et al. 2011; Li et al. 2008).

The stimulation of FOXO3-p53 interactions and the binding of the stimulated FOXO3 into the apoptotic genes p53 and p27 by the flavonoid, may indicate to the benefit of the combined use of the genistein rich foods/plants; kudzu, soybean, favabeani lupine, psorolea and miso with FOXO3 inducing anti-cancer drugs; metformin, doxorubicin, nipradilol, timolol, melatonin, withhaferin A, bortezomib, vorinostat, tunicamycin, paclitaxel, geldanamycin, AZD5363, cisplatin and 5-aza-2-deoxycytidine and also vitamins C and B rich foods; e.g. banana, broccoli, fresh cabbage, fresh spinach, tomato, lettuce, citrose fruits, green leafy, carrot, amaranth, guava, mango, papaya, sugarapple, strawberry, cucumber, green chili, red chili, mint, French bean and finally resveratrol rich foods; e.g. peanuts, grapes and blueberries, since

all the mentioned flavonoids, vitamins and anti-cancer drugs may form a synergy to induce FOXO3.

DNA repair pathways as a response to the anti-cancer treatments to survive DNA damage primarily involves signaling cascades comprise the DNA-dependent protein kinase (DNA-PK), Ataxia-telangiectasia mutated (ATM), ATM and Rad3 related (ATR) and checkpoint kinases 1 and 2 (Chk1/Chk2), the enzymes, all of which repair DNA (Perona et al. 2008). On the other hand, the increased abundance and overactivation of the tumor suppressor gene, E2F1, triggers invasion and metastasis by activating growth receptor signaling pathways which may promote an antiapoptotic tumor environment and hence, may form chemoresistance (Engelmann and Putzer 2012). But, the inhibition of E2F1 by the flavonoid (Lu et al. 2000), may be useful during such chemotherapies, though there is no data as related to the anti-cancer flavonoid and E2F1 associations.

The combined use of the flavonoid and the anti-cancer bioactive food compounds which target cancer cells by activating the apoptotic gene, BRCA1; genistein (Tominaga et al. 2007), indol-3-carbinol (Fan et al. 2006), resveratrol ((Fustier et al. 2003), curcumin (Jain 2015) and sulforaphane (Yi et al. 2014), may have stronger anti-cancer potential than their administrations per se, since all these three flavonoids and genistein may form a synergy to kill cancer cells by inducing BRCA1 expression. Therefore, the combined consumption of the foods/plants rich in these 4 bioactive components; kudzu, soybean, favabean, lupine, psorolea, miso, white cabbage, broccoli, red cabbage, cauliflower, Brussels sprouts, radish, mustard, turnip, Chinese kale, peanuts, grapes, blueberries, *Curcuma longa*, cinnamon, cinnamon containing foods and bok choy may be useful in the anti-cancer diet. But, an important point currently is the lack of knowledge as related to the effects of the other bio-active food and plant compounds other than these four ones and anti-cancer drugs on BRCA1 to form a much more accurate anti-cancer diet which may get alone well with the administered anti-cancer foods or drugs.

The inhibitory effect of genistein on the anti-apoptotic proteins; Cdc25A and Cdc25C may enhance the anti-cancer potential of the treatments which administer Cdc25 inhibitors; K252a (Chin et al. 1999),

NSC 663284 (Pu et al. 2002), NSC 95397, monohydroxyl-NSC 95397, dihydroxyl-NSC 95397 (Peyregne et al. 2005), mpV (phosphotyrosine phosphatase inhibitor) (Brenner et al. 2014), BN82002 (Brezak et al. 2004), hexaprenylhydroquinone (Han et al. 2004). Accordingly, involvement of the genistein rich foods and plants; kudzu, soybean, favabean, lupine, psorolea and miso, into the anti-cancer diet during the treatments with the mentioned Cdc25 inhibitors, may be useful, creating a synergy via the inhibition of Cdc25 proteins.

The other anti-cancer effect of the flavonoid may be due to its inhibitory effect on ERalpha when it is at $>10^{-5}$ M concentrations (Marik et al. 2011; Wang et al. 1995; Shao et al. 1998). The important point to be considered is that the flavonoid has got the opposite effect, inducing the receptor at the lower concentrations (Hsieh et al. 1998). Thus, the flavonoid rich foods/plants, e.g. kudzu, soybean, fava bean, lupine, psorolea and miso in the anti-cancer diet may enhance the anti-cancer potential of the ERalpha inhibitors; nafoxidine, hexestrol, C1618 and dienstrol, in addition to vitamin C and resveratrol rich foods, e.g. peanuts, grapes, blueberries, banana, broccoli, fresh cabbage, grapefruit, fresh spinach, tomato, lettuce, citrose fruits (e.g. orange, lemon..) and green leafy since all the mentioned anti-cancer drugs, the flavonoid and the vitamin, may form a synergy by inhibiting ERalpha, like genistein. This detail may be more crucial, especially in the diet of the patients with breast cancer.

The flavonoid may also show anti-cancer effect by inhibiting ERK signaling, NF-kB (nuclear factor kappa-light-chain enhancer of activated B cells, the protein which controls transcription of DNA while its overactivation styimulates cancer (Staudt 2010). Therefore, the anti-cancer drugs which inhibit NF-kB; emetine, fluorosalan, sunitinib malate, bithionol, narasin, tribromsalan, lestaurtinib, ectinascidin 743, chromomycin A3 and bortezomib, all of whose NF-kB inhibitory effects are determined by Miller et al. (2010) and the anti-cancer drugs which show anti-cancer effect by inhibiting ERalpha; nafoxidine, hexestrol, C1618 and dienestrol, may have stronger anti-cancer potential if they are administered with an anti-cancer diet which involves genistein rich foods/plants; e.g. kudzu, soybean, fava bean, lupine, psorolea and miso

since the mentioned anti-cancer drugs and the flavonoid may form a synergy to inhibit NF-kB and ERalpha.

The inhibition of the activity of COX-2 (cyclooxygenase-2), the enzyme which is responsible for the production of inflammatory hormones while inhibiting the antiapoptotic hormone, IGF whose actions are mediated via the PI-3 kinases, the enzymes which are involved in cell growth and survival, by the flavonoid, is the other anti-cancer and anti-inflammatory effect of the flavonoid (Ye et al. 2004; Swami et al. 2007). This effect of the flavonoid may enhance the anti-cancer drugs which similarly inhibit COX-2, namely; sunitinib, celecoxib, magnolol, honokiol, eugenol, bis-eugenol, tetrandrine, 17AAG, raloxifene, rofecoxib, nafroxen, dexamethasone, hydrocortisone, triamcinolone acetonide, methyl prednisolone and beclomethasone diproprionate, creating a synergy to inhibit COX-2 activity.

Genistein inhibits the anti-apoptotic ERK signaling, like vitamin C and therefore, the consumption of both genistein and vitamin C rich foods/plants; kudzu, soybean, favabean, lupine, psorolea, miso, banana, broccoli, fresh cabbage, grapefruit, fresh spinach, tomato, lettuce, citrose fruits and green leafy, may be useful to enhance the anti-cancer potential of vorinostat, lapatinib, fulvestrant, PD98059, UO126, honbokiol, all of which similarly inhibit the signaling and hence may form a synergy with the flavonoid. Additionally, broccoli, fresh cabbage, radish, mustard, Brussels sprouts, cauliflower, Chinese kale and turnip, may be useful during the treatments with the mentioned ERK inhibitors since these foods are rich in sulforaphane which inhibits the signaling like genistein and vitamin C.

One of the anti-cancer effect mechanisms of the flavonoid is its inhibitory effect on another anti-apoptotic signaling, Hedgehog (Hh) which transmits information to embryonic cells for the cell development and survival (Slusarz et al. 2010). This effect of the flavonoid is also confirmed for breast cancer, prostate cancer and gastric cancer (Fan et al. 2013; Zhang et al. 2012 and Yu et al. 2014). So, the genistein rich foods/plants, e.g. kudzu, soybean, favabean, lupine, psorolea, miso, may be useful during the treatments with the anti-cancer drugs; SANT-1-SANT4, CUR-61414, HhAntag-691, GDC-0449, guggulsterone, saridegib, phthaladines (e.g.LY2940680, NVP-LEQ506),

itracanazole, NVP-LDE225, TAK-441, XL-139, HTS piperidines, MRT-92, MRT-83, PF-04449913, N-acylethanolamides, 2-acylglycerols and 2-alkylglycerol, since the mentioned anti-cancer drugs and the flavonoid, may form a synergy to inhibit the signaling. This effect of the flavonoid is also confirmed for breast cancer, prostate cancer and gastric cancer (Fan et al. 2013; Zhang et al. 2012 and Yu et al. 2014). So, the genistein rich foods/plants, e.g. kudzu, soybean, favabean, lupine, psorolea and miso, may be useful during the treatments with the anti-cancer drugs; SANT1-SANT4, CUR-61414, HhAntag-691, GDC-0449, guggulsterone, saridegib, phthaladines, itracanozole, NVP-LDE225, TAK-441, XL-139, HTS piperidines, MRT-92, MRT-83, PF-04449913, N-acylethanolamides, 2-acylglycerols and 2-alkylglycerol, since the mentioned anti-cancer drugs and the flavonoid may form a synergy to inhibit the signaling.

The effect of the flavonoid on Hem oxygenase-1 (HO-1) which produces cancerogenic teratogens may be one of the reasons for the anti-cancer potential of the flavonoid. The flavonoid increases the expression of the anti-apoptotic protein, Hem oxygenase-1 and this effect markedly reduces the LDL (Low Density Lipoprotein)-induced MCP-1 (Monocyte chemoattractant protein-1, one of the key chemokines that regulates migration and infiltration of monocytes/macrophages), VCAM-1 (Vascular cell adhesion molecule-1, the gene which mediates the adhesion of lymphocytes, monocytes, eosinophilis to vascular endothelium) and ICAM-1 (Intercellular Adhesion Molecule 1), the protein which facilitates leucycte endothelial transmigration (Zhang et al. 2013). Confirmingly, the findings of Zhang et al. (2013) indicate to the atherosclerotic effect of the flavonoid as a result of its inducing effect on HO-1, leading to the overexpression of the anti-apoptotic protein. Therefore, the anti-cancer treatments which administer HO-1 inhibitors; tin (IV) protoporphyrin 1 dichloride (SnPP), zinc (II) protoporphrin IX (ZnPP), zinc (II) deuteroporphyrin IX-2, 4 bisethyleneglycol, imidazole-based compounds (8, 9,10R,10S,11,12,13,3), caveolin-1, calcineurin, siRNA, metformin, tin-mesoporphyrin, zinc mesoporphyrin (ZnMP), PEG-ZnPP (pegylated zinc protoporphyrin) and OB-24, may be contraindicated with the genistein rich foods/plants, e.g. soybean, fava bean, kudzu, lupine, psorolea and miso.

The STUDIES about GENISTEIN and it's ASSOCIATION with CANCER

- 652 control / 261 ovarian cancer / 1990-2000 / smoking adjusted, alcohol adjusted / ≥20.9 mg/d (0.50, 0.30-0.84, 95% CI) versus ≤6.6 mg/d (R:1.00, 95% CI) decreased the risk of ovarian cancer (Zhang et al. 2004).
- 64327 women / 1988-2003 / alcohol adjusted, smoking adjusted / soybean curd (almost everyday) (0.61, 0.26-1.45, 95% CI) versus no soybean curd consumption (R:1.00, 95% CI) decreased the risdk of ovarian cancer (Sakauchi et al. 2007).
- 97275 women / 1995-2003 / 35-84 years of age / alcohol adjusted, smoking not / ≥1.1 mg/d (0.65, 0.42-1.02, 95% CI) versus ≤0.3 mg/d (R:1.00, 95% CI) did not make any change on the risk of ovarian cancer (Chang et al. 2007).
- 36.177 men and 40.484 women / 5 year of follow up / 45-74 years of age / smoking adjusted, alcohol adjusted / 48 mg/d (0.89, 0.67-1.19, 95% CI) versus 9 mg/d (R:1.00, 95% CI) decreased the risk of lung cancer in never smokers!!(Shimazu et al. 2010).
- 73.223 women / 592 breast cancer / 7.4 years of follow-up / 40-70 years of follow-up / alcohol adjusted, smoking not / the highest quartile of soy isoflavones (0.86, 0.65-1.13, 95% CI) versus the lowest (R:1.00, 95% CI) decreased the risk of breast cancer in adolescence and adulthood in women, but not make any difference in postmenopausal breast cancer (Lee et al. 2009) (The amounts of soy isoflavones are not mentioned while the study does not analyse the sole effect of genisten, instead, total soy isoflavones !!.
- 256 patient with breast cancer / 2004-2011 / 46.7 ± 9.4 median age / smoking adjusted, alcohol adjusted / >35.30 mg/d (0.25, 0.09-0.54, 95% CI)) versus <8.45 mg/d (R:1.00, 95% CI) reduced the risk of breast cancer (but again, total soy isoflavone intake was studied instead of the sole administration of genistein!) (Kang et al. 2012).

- 393 control / 131 patients with gastric cancer / smoking adjusted, alcohol adjusted / 62.8-63.7 median age / 1993-2004 / 229 nmol/L plasma genistein (0.54, 0.31-0.93, 95% CI) versus 181.8 nmol/L in patients with gastric cancer (R:1.00, 95% CI) decreased the risk of gastric cancer (Ko et al. 2010)
- 1978-2004 / 6 cohorts, a meta-analysis / high-soy intake decreased the risk of breast cancer (0.86, 0.75-0.99, 95% CI), especially in premenopausal women (Trock et al. 2006)
- 2280 women / 282 breast cancer / 6.31 years of follow up / smoking adjusted, alcohol not / 18-79 years of age / ≥13.025 mcg/d (1.75, 0.65-4.76, 95% CI) versus no genistein intake (R:1.00, 95% CI) did not make any change while ≥9596.55 mcg/d daidzein (0.43-4.95, 1.45, 95% CI) versus no daidzein intake (R:1.00, 95% CI) decreased the risk of breast cancer (Guha et al. 2009)
- 24226 women / 40-69 years of age / 10.6 years of follow up / 144 breast cancer / smoking adjusted, alcohol adjusted / 78.8-255.6 ng/mL (0.62, 0.21-1.84, 95% CI) versus 67.9-202.6 ng/mL (R:1.00, 95% CI) decreased the risk of breast cancer (Iwasaki et al. 2008)
- 150000 men / 1992-2000 / 1605 prostate cancers /44-85 years of age / alcohol adjusted, smoking adjusted / 412 ng/mL (1.9, 0.2-30.1, 95% CI) genistein plasma concentration versus 40 ng/mL (0.3, 0.05-5.05, 95% CI) did not make any change on the risk of prostate cancer (Travis et al. 2012)
- 14105 men / 28 prostate cancer / 1988-2002 / smoking adjusted, alcohol not / >682 nM plasma genistein concentration (0.54, 0.32-1.82, 95% CI) versus <239 nM (R:1.00, 95% CI) decreased the risk (Ozasa et al. 2004)

LYCOPENE

Lycopene, the bright red carotene and carotenoid pigment and phytochemical, is found as richest in tomatoes (Shi and Le Maguer 2000), red carrot (Horvitz et al. 2004), watermelon (Edwards et al. 2003); gac (Kubola et al. 2013), papayas (Devitt et al. 2010), strawberries (Ilic et al. 2011), guava (Kong et al. 2010), green pepper, sweet pepper, bell pepper, cayenne pepper (Adebisi et al. 2014), red cabbage, asparagus (Alda et al. 2014) and mango (Gouado et al. 2007).

The association of lycopene with various cancers including prostate, lung and gastric cancers and the decrease in the risk of occurrence of these cancers due to the antioxidant effect of it is well documented (Takeoka et al. 2001; Kelkel et al. 2011; Rao et al. 2000; Martinez-Valverde et al. 2002; Wei and Giovannucci 2012; Arab et al. 2002; Liu and Russell 2008).

Unlike of many bioactive compounds, lycopene prevents reactive oxygen-mediated apoptosis and inhibits ROS generation (Krishnamoorthy et al. 2013; Palozza et al. 2011; Kumavat and Chaudhari 2013; Kim and Kim 2015; Zou et al. 2013). Therefore, the anti-cancer drugs which cause apoptosis by inducing ROS like; sunitinib, sorafenib, tetrandine, cisplatin, bortezomid, vorinostat, MG-132, metformin, thapsigargin, tunicamycin, 17AAG, DBeQ, ritonavir and brefeldin A, may show less anti-cancer potential if lycopene rich foods; tomatoe, red carrot, gac, papaya, watermelon, guava, pepper, red cabbage, asparagus and mango are consumed heavily and regularly during the treatments by the mentioned anti-cancer drugs. Although, the strong activity of the quenching the singlet oxygen may contribute to cancer prevention in people without cancer, the same attribute of the bio-active compound may decrease the anti-cancer potential of the anti-cancer drugs since they induce apoptosis by producing ROS, opposite to lycopene.

The bio-active compound reduces the phosphorylation of Akt and suppress Akt signaling, the signaling by the serine/threonine-specific protein kinase that plays a key role in apoptosis, but also in cell proliferation including cancer cells, especially by phosphorylating

the OH group on the side chain of a serine or threonine amino acid residue in a protein with a phosphate group from ATP (Tang et al. 2008). Lycopene also inhibits the signaling of the complex of 'Akt and PI3Ks' which are the major effectors which downstream of receptor tyrolysine kinases and transducer signals from growth factors and cytokines into intracellular messages by generating phospholipids, which in turn activates AKTs, Membrane Metalloproteinase-2 (MMP) and Urokinase plasminogen activator (UPA to regulate cell proliferation and embryonic development, mediated through VEGFR2 (Chen et al. 2012). The compound also suppresses cyclin D1, one of the cyclins that regulate activity of Cyclin-dependent kinases (CDKs) for cell cycle progression while inhibiting Akt/PI3K signaling (Tang et al. 2008). So, CDK inhibitors may benefit from a lycopene rich food consumption, the inhibitors like; aloisine, [RP 106,7-n-Butyl-6-(4-hydroxyphenyl) [5H]pyrrolo[2,3-b]pyraizne],aloisineA [RP107,7-n-Butyl-6-(4-hydroxyphenyl)[5H]pyrrolo[2,3-b]pyraizne], alsterpaullone[9-Nitro-7, 12-dihydroindolo-[3,2-d][1]benzazepin-6(5H)-one], 3-Amino-1H-pyrazolo[3,4-b]quinoxaline, 3-ATA(3-amino-9-thiol[1OH]-acridone), Benfluorene [Ethyl-(6-hydroxy-4-phenylbenzo[4,5]furo[2,3-b]pyridine-3-carboxylate; 1-Aza-9-oxafluorene5a], bohemine [6-benzylamino-2-(3-hydroxypropyl-amino)-9-isopropylpurine], 2-bromo-12,13-dihiydro-5H-indolo[2,3-α]pyrrolo[3,4-c]carbazole-5,7(6H)-dione, CGP74514A [N-(cis-2-aminocyclohexyl)-N-(3-chlorophenyl)-9-ethyl-9H-purine-2,6-diamine], 3-(2-chloro-3-indolymethylene)-1,3-dihydroindol-2-one, compound 52, CVT-313[6-(4-methoxybenzylamino-2-[bis(2-hydroxymethylamino)]-9-isopropylurine], 9-cyanopaullone [9-cyano-7,12-dihydroindolo-[3,2-d]benzazepin-6[5H]-one], debromohymenialdisine [DBH;4-(2-amino-4-oxo-2-imidazolin-5-ylidene)-4,5,6,7-tetrahydropyrrolo[2,3-c]azepin-8-one], Elbfluorene [3-acetyl-6hydroxy-4-phenylbenzol[4,5]furo[2,3-b]pyridine; 1-Aza-9-oxafluorene 5b], Fascaplysin (dehydroluffarielloide diacid monoanion), 10Z-hymenialdisine[4-(2-amino-4-oxo-2-imidazolin-5-ylidene)-2-bromo-4,5,6,7-tetrahydropyrrolo azepin-8-one], hymenidin[2-debromooroidin], indirubin-3-monoxime (C16H11N302), N-6-(delta2-isopentenyl)-adenine[6-ϒ,ϒ-dimetylallylamino)purine], kenpaullone [9-bromo-7,12-dihydroindolo-[3,2-d]benzazepin-6(5H)-one],

NU2058 [O6-cycloexylmethylguanine], olomoucine[6-benzylamino-2-(2-hydroxyethylamino)-9-methylpurine], PNU 112455A.HCl [N4-(6-aminopyrimidin-4-yl)-sulfanilamide.HCl)], purvalanol A[6-[(3-chloroanilino]-2(1R)-isopropyl-2-hydroxyethylamino)-9-isopropylpurine], roscovitine [6-benzylamino-2-®-[(1-ethyl)-2-hydroxyethylamino]-9-isopropylpurine], staurosporine (C28H26N403), SU9516[3-[1-(3H-Imidazol-4-yl)-meth-(Z)-ylidene]-5-methoxy-1,3-dihydro-indol-2-one], TG02 (also known as SB1317)(C23H24N4O), sorafenib, toyocamycin, bortezomib (which also blocks the activation of CDK by docetaxel as one of the side effects of the anticancer drug), 17 AAG, radicicol, paclitaxel, NU6140, tetrandrine, metformin, honokiol and palbociclib. The fact that the flavon inhibits PI3K, Akt and the signaling of Akt/PI3K and Akt inhibitors; wortmannin, piceatannol, IC-87114, myricetin, quercetin, staurosporine, PIK-75, WHI-p154, WHI-P131, CAL-101, GSK2126458, fisetin, 17-β-hydrocywortmannin, miltefosine, perifosine, NVP-BEZ235, rosiglifazone, CH5132799, CAY10505, 3,4,7-trihydroxyisoflavone (one of the metabolites of daidzein), PIK90, compound 15e, PIK-294, GSK1059615, PP121, PX-866, SF1126, PF-05212384, sunitinib, sorafenib, cisplatin, tetrandrine, ICI182.780, LY29002, SF-1126, NVP-BEZ235, XL147, XL765, ISC-4, GSK690693, MK2206, fused pyrimides, PIP3, GDC-0941, celecoxib, UCN-01, BX-795, BX-912, BX-320, CCT128930, GDC-0068, perifosine, GSK-214795, BX-320, GSK2110183, ipatasertib, afuresertib, AT13148, PF-04691502, A47867 and triciribine, creating a synergy of both the carotenoid and the anti-cancer drugs via the inhibition of PI3K and Akt.

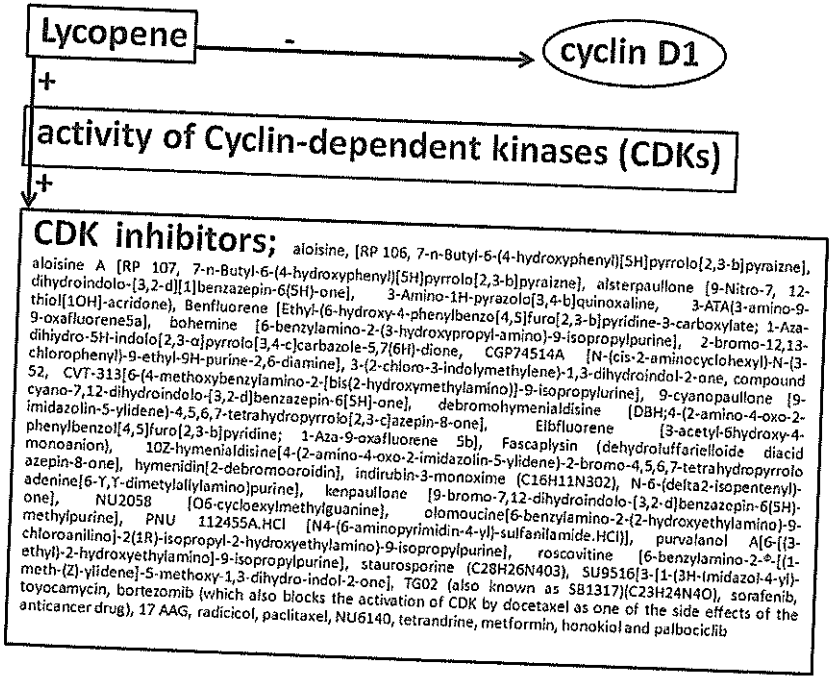


FIGURE 65

The phytochemical's one important effect against cancer is its inhibitory effect on COX-2, the enzyme which produces inflammatory and cancerogen hormones, expression through the heme oxygenase-1 (HO-1)(the enzyme which produces teratogens) inducible nitric oxide/synthase (iNOS) (the enzyme which produces NO, modulating angiogenesis and metastasis) and interleukin (IL-6) (which induces inflammation, promoting angiogenesis and tumor growth) (Feng et al. 2010; Rafi et al. 2007; Lin et al. 2014; Doi et al. 2015; Kang et al. 2011; Lv et al. 2015; Sung et al. 2015). Therefore, the anti-cancer potential of the IL-6 inhibitors; tocilizumab, sunitinib, sorafenib, metformin, radicicol, 17-AAG, monensin, brefeldin A, raloxifene, bortezomib, siltuximab, honokiol, curcumin, HO-1 inhibitors; tin (IV) protoporphyrin 1 dichloride (SnPP), zinc (II) protoporphrin IX (ZnPP), zinc (II) deuteroporphyrin IX-2, 4 bisethyleneglycol, imidazole-based compounds (8, 9,10R,10S,11,12,13,3), caveolin-1, calcineurin, siRNA, metformin, tin-mesoporphyrin, zinc mesoporphyrin (ZnMP), PEG-ZnPP (pegylated

zinc protoporphyrin) and OB-24, Cox-2 inhibitors; sunitinib, celecoxib, magnolol, honokiol, eugenol, rofecoxib, nafroxen, dexamethasone, hydrocortisone, beclamethasone diproprionate, and iNOS inhibitors; ; L-arginine, L-canavanine, L-NAMA (NG-nitro-L-arginine methyl ester hydrochloride), L-NNA (L-NG-nitroarginine), N6, NG-dimethyl-L-arginine, L-NIL [L-N6-(1-iminoethyl) lysine dihydrochloride], NILT (N6-iminoethyl-lysine tetrazoleamide), L-NIO [N(5)-(-(-iminoethyl)-L-ornithine], vinyl-L-NIO, AMT(2-amino-5,6-dihydro-6-methyl-4H-1,3-thiazine), L-thiocitrulline, S-methyl-L-thiocitrulline, N-propyl-L-arginine, 1400W, A-guanidiglutaric acid, S-(2-aminoethyl)isothiourea, EIT hydrobromide, Mercaptoethylguanidine, S-ethylisothiourea, S-methylisothiourea, 1,3-PBIT) [1,3-S,S-1,4-phenylenebis (1,2-ethanediyl)bis-isothiourea], 1,4-PBIT, Aminoguanidine, 2-imino-4-methylpiperidine, TRIM (1-[2-trifluoromethylphenyl] imidazole, 7-nitroindazole, 3-bromo-7-nitroindazole and BYK-191023 dihydrochloride (2-[2-(4-Methoxy-2-pyridinyl)ethyl]-1H-imidazol [4,5-b] pyridine dihydrochloride) may be enhanced if an anti-cancer diet rich in lycopene is followed during the treatments with the mentioned inhibitors, creating a synergy via the inhibition of COX-2, IL-6, iNOS and HO-1 activities.

Mitogen-activated protein kinases (MAPK), the protein kinases which are specific to the amino acids; serine, threonine and tyrosine and relay extracellular signals for cell proliferation and differentiation, are also inhibited by the phytochemical. The well known MAPKs are; ERK1/2, p38, JNK and IL-8, the cytokine which has a promoting effect on angiogenesis and improving effect on antiapoptotic gen expression (Kim et al. 2004; Li et al. 2004; Lv et al. 2015; Heideman et al. 2003). Especially, the approach as the inhibition of IL-8, the cytokines which are responsible for the angiogenesis and antiapoptotic gen expression, has appeared as one of the novel anti-cancer treatments, using IL-8 inhibitors like; reparixin (Leither et al. 2007), lidocaine (Lahav et al. 2002), SC-514, PS-341, MG-132 (Lee et al. 2013), SB-225002 (White et al. 1998), imatinib (Ciarcia et al. 2012), erythromycin, clarithromycin (Kohyama et al. 1999), G06976 (a protein kinase inhibitor) (Pan et al. 2006), diaryl imidazoles (Crawford et al. 2008), Azelastine (Kempuraj et al. 2003), celastrol (Youn et al. 2014), sunitinib (Huang et al. 2010),

sorafenib (Park et al. 2015), cisplatin (Li et al. 2015), tetrandrine (Wu and Nq 2007), thapsigargin (Elferink and de Koster 2000), ritonavir (Pati et al. 2002), metformin (Isoda et al. 2006), tamoxifen (Bendrik and Dabrosin 2009), honokiol (Wang et al. 2015). These IL-8 inhibitors may have stronger anti-cancer effect if an anticancer diet rich in lycopene containing the foods; tomatoe, red carrot, watermelon, gac, papaya, strawberries, guava, green pepper, sweet pepper, bell pepper, cayenne pepper, red cabbage, asparagus and mango, since lycopene with its inhibitory effect on IL-8 may form a synergy with the mentioned IL-8 inhibitors. But, it is a crucial point to be concerned during the anti-cancer treatments using the IL-8 inhibitors. The involvement of the lycopene rich foods into the anti-cancer diet may be much more beneficial with paclitaxel, bevacizumab, bortezomib, darunavir, ritonavir, lopinavir and atazanavir because their their IL-8 inducing effects (Auclair et al. 2014; Manna et al. 2013; Gyanchandani et al. 2013; Uslu et al. 2005), as one of the side effects of the mentioned anticancer drugs, may be inhibited by the consumption of lycopene rich foods. It should especially be noted that green tea should be better avoided since it induces IL-8 expression (Netsch et al. 2006) which may worsen the prognose of the anti-cancer drugs which similarly induce IL-8 and while decreasing the former group of anticancer drugs which inhibit IL-8 secretion.

JNK, c-Jun NH2-terminal kinase, a mitogen-activated kinase (MAPK), may be a proto-oncogen but also a tumor suppressor. The oncogenic activity of the MAPK comes from its task to phosphorylate c-Jun at serine-63 and serine-73, the sites which are essential to stimulate of c-Jun activity for oncogenic transformation (Tournier 2013). But, the dual action of the MAPK depends on the intensity and kinetics of the JNK signal that Bcl-2, associated with Beclin-1 (which are both antiapoptotic proteins), is more readily phosphorylated by JNK in the case of the higher intensity and kinetic of the signal than when it is in complex with Bax (another antiapoptotic protein) in case of the poor intensity and kinetic of the signal and this mechanism switches JNK from a proautophagic/prosurvival to a proapoptotic/prodeath function. The more readily phosphorylation of Bcl-2/Beclin-1 complex by JNK is a transient JNK activation which promotes cell survival, while the binding of JNK to Bax is a prolonged JNK activation which induces

apoptosis (Ventura et al. 2006). The crucially important point here is that inhibition of JNK sensitizes tumor cells to apoptosis induced by CD95 (a member of the tumor necrosis factor receptor superfamily) (Kuntzen et al. 2005), leading to G2/M cell cycle arrest. On the other hand, lycopene increases the expression of Bax (Palozza et al. 2010; Trejo-Solis et al. 2013), leading to the increase in Bax and Jun complex which results in apoptosis. Also, the inhibitors of the proto-oncogen proteins, BRAF, suppress JNK activity through the inhibition of ZAK, MKK4 and MAP4K5 (all of which are activated protein kinases) (Vin et al. 2013).

Both Tumor Necrosis Factor (TNF), JNK and NFkB (the protein complex that controls transcription of DNA, cytokine production and cell survival) activation stimulates survival and proliferation (Volk et al. 2014). Therefore, the anticancer effect of the NF-kB and TNF inhibitors; emetine, fluorosalan, sunitinib malate, bithionol, narasin, tribromsalan, lestaurtinib, actinasadin 743, chromomycin A3, bortezomib, infliximab, etanercept, adalimumab, certolizumab, golimumab, tetrandrine, honokiol, vorinostat, celecoxib, naproxen, indomethacin, sulindac, dexamethasone, curcumin, tamoxifen, resveratrol, green tea and/or EGCG, the JNK inhibitors; SP600125, piceatannol, CC-401, RWJ67657, AS602801, JNK-IN-8 and TNF and JNK inhibiting effect of lycopene (Simone et al. 2011; Palozza et al. 2010; Kim et al. 2004; Lv et al. 2015; Hung et al. 2008; Di Tomo et al. 2012), may be enhanced with lycopene rich foods. Additionally, beta-carotene rich foods; carrot, amaranth, guava, mango, orange, papaya, strawberry, sugar apple, cucumber, green chili, red chili, cabbage, spinach, tomato, lettuce, mint and French bean, may increase the anticancer potential of the mentioned TNF-inhibiting drugs and lycopene since beta-carotene also inhibits TNF (Di Tomo et al. 2012), creating a synergy with the anti-cancer drugs and lycopene. Similarly; coumarin rich foods/plants; cinnamon, cinnamon containing foods and Curcuma longa, resveratrol rich foods; grape, blueberries, raspberries, mulberries, turmeric, ginger, EGCG rich foods/plants; white tea, green tea, dark chocolate, fava bean, pear, raspberries, cherries, blackberries and apple, may also be beneficial to be included during the treatments that target cancer by inhibiting TNF, since these three flavonoids also inhibit TNF. Especially, the anticancer

treatments which target the inhibition of TNF-α, using the specific TNF-α inhibitors; lenalidomide (corral et al. 1999), TNF-α antagonist (Suzuki et al. 2006), SIRT1(Moon et al. 2013), 2-palmitylglycerol (Gallily et al. 2000), MIF(ISO-1) (West et al. 2008), sulfasalazine (Shanahan et al. 1990), R-7050 (King et al. 2013), CGP41251 (Si et al. 2005), Thalidomide (Deng et al. 2003), betulin, betulinic acid (Szuster-Ciesielska et al. 2011), pomalidomide (Galustian et al. 2009), CAY10500 (Zhao et al. 2014), N-stearoyl-phytosphingosine (SPS) (Ryu et al. 2010), 17®HDoHE, AT-RvD1 (Xu and Ji 2011), quinolactacin A (Sasaki et al. 2006) and quinolactacin B(Tatsuta et al. 2001) may benefit from the anticancer diet rich in lycopene, coumarin, curcumin, resveratrol and EGCG, the flavonoids, all of which inhibit TNF-α, creating a synergy with the specific TNF-α inhibitors.

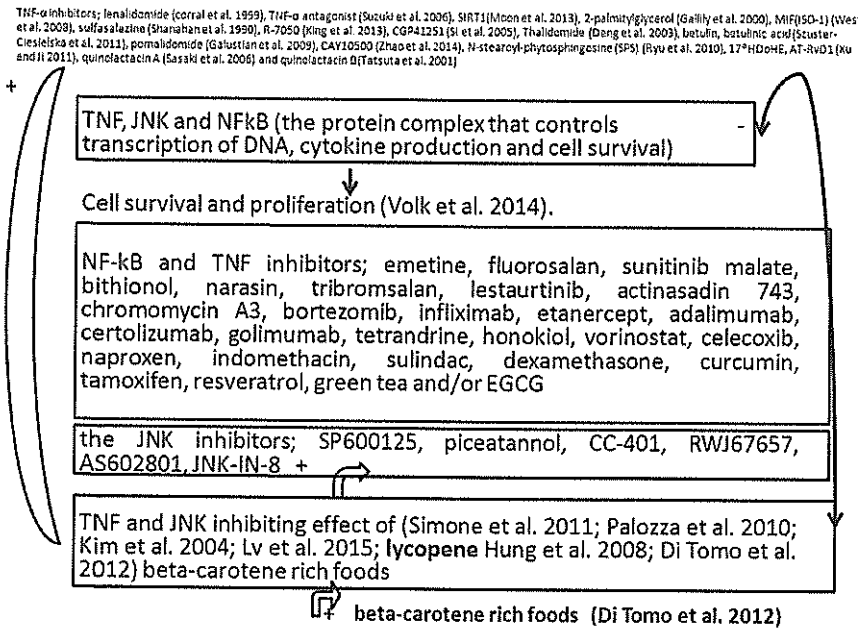
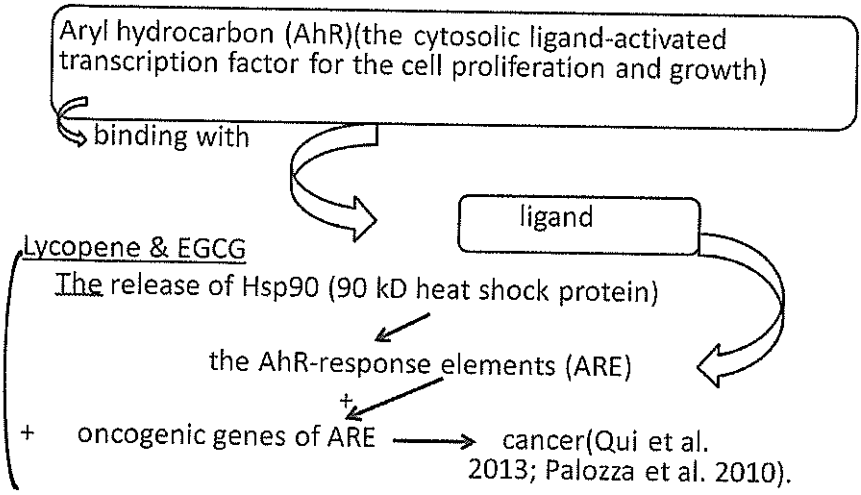


FIGURE 66

Aryl hydrocarbon (AhR), the cytosolic ligand-activated transcription factor for the cell proliferation and growth, is not bound any ligand. When it binds to a ligand, Hsp90 (90 kD heat shock protein) is released

and the ligand in AhR binds to the AhR-response elements (ARE) and this binding affects the transcription of the oncogenic genes of these elements. Briefly, the release of Hsp90 activates the oncogenic genes in AhR and directly initiates cancer. On the other hand, lycopene down-regulates and inhibit the chaperon, Hsp90, inhibiting the release of this chaperon and subsequently the activation of the oncogenic genes in AhR while the same chaperon, Hsp90, is also crucial for the protein folding capacity and functionality of tumor cells (Qui et al. 2013; Palozza et al. 2010). Thus, the inhibition of Hsp90 by a lycopene rich nutrition, may enhance the anticancer potential of the Hsp90 inhibitors; geldanamycin, 17AAG, tanespimycin, 17-DMAG (geldanamycin analog), 17-AG (17-amino-17-demethoxygeldanamycin; IP-493), trastuzumab, IPI-504, radicicol, AT13387, PU-H71, AICAR (5-aminoimidazole-4-carboxamide-1-β-D-ribofuranoside), herbimycin A, gedunin, celastrol, NVP-AUY922, HSP-990, KU135 (novobiocin-derived C-terminal Hsp90 inhibitor), novobiocin, macbecin, ganetespib, MPC-3100, benzisoxazole Hsp90 inhibitor, 17-GMB-APA-GA, 17-AEP-GA, 17-DMAP-GA, KW-2478, NVP-BEP800, B11B021, nelfinavir mesylate, VER-50589 and VER-49009, honokiol and also cytarabine, carboplatinum, toptecan, vincristine, cyclophosphomide, cisplatin, methotrexate and etoposide, the chemotherapeutic agents which are in synergism with AAG to inhibit Hsp90 and finally shepherdin, pochonin, radester, PU-3 and PU24FCl. An important detail to concern here is the crucial necessity of nucleotides in the regulation of Hsp90 structure and function (Young et al. 2001). For example, adenosine triphosphate (ATP) binds to Hsp90 which is essential to stimulate Hsp90 since only after this binding, p23, one of the co-chaperons of Hsp90, binds Hsp90 and activates it (Weikl et al. 2000; Felts and Toft 2003). Neither a possible inhibitory effect of lycopene nor the most of the anticancer agents namely sunitinib, sorafenib, thapsigargin, cisplatin, vorinostat, bortezomib, MG-132, tunicamycin, tamoxifen, versipelostatin, toyocamycin and tetrandrine is presently known. Further studies are needed to highlight the anticancer effect of the flavonoid and the anticancer effect of the flavonoid and the anticancer drugs via the p23 inhibition. Also, out of the flavonoids, the associations of I3C, quercetin, kaempferol and apigenin with p23 need to be highlighet while EGCG and resveratrol inhibit p23 (Lee

2010; Chinta et al. 2009), curcumin up-regulates it (Goel et al. 2008) and sulforaphane has no effect on this gene (Li et al. 2012). Another missing and unknown point about the flavonoid currently is the effect of the flavonoid on the Hedgehog signaling, the signaling of selfrenewal and tumorigenicity.



the inhibition of Hsp90 by a lycopene rich nutrition, may enhance the anticancer potential of the Hsp90 inhibitors; geldanamycin, 17AAG, tanespimycin, 17-DMAG (geldanamycin analog), 17-AG (17-amino-17-demethoxygeldanamycin; IP-493), trastuzumab, IPI-504, radicicol, AT13387, PU-H71, AICAR(5-aminoimidazole-4-carboxamide-1-β-D-ribofuranoside), herbimycin A, gedunin, celastrol, NVP-AUY922, HSP-990, KU135(novobiocin-derived C-terminal Hsp90 inhibitor), novobiocin, macbecin, ganetespib, MPC-3100, benzisoxazole Hsp90 inhibitor, 17-GMB-APA-GA, 17-AEP-GA, 17-DMAP-GA, KW-2478, NVP-BEP800, BIIB021, nelfinavir mesylate, VER-50589 and VER-49009, honokiol and also cytarabine, carboplatinum, topotecan, vincristine, cyclophosphomide, cisplatin, methotrexate and etoposide, the chemotherapeutic agents which are in synergism with AAG to inhibit Hsp90 and finally shepherdin, pochonin, radester, PU-3 and PU24FCl

FIGURE 67

One of the anticancer effects of the flavonoid is via the induction of caspase activity, especially caspase 3, which results in proteolyzis of DNA and subsequently, apoptosis (Venier et al. 2012). As a result, the involvement of lycopene rich foods into the anticancer diet may enhance the anticancer potential of costunolide, mitomycin c, garcinol, valinomycin, piceatannol, kinetin riboside, lipase inhibitor, THL (tetrahydrolipstatin), imiquimod, SC560, romidepsin, ouabain, digoxin, proscillaridin A, borrelidin, sanguinarine, MT-21, ionidamine, K858, saikosaponin A, CIL-102 and prodigiosin, brefeldin A, cisplatin, creating a synergy to induce caspase activity which permeabilizes the

outer mitochondrial membrane by leading to ROS influx, cytochrome c release and proteolyzes of DNA.

The carotenoid inhibits NO (Rafi et al2007; Selvan et al. 2011). As previously having been analyzed in detail in the part of vitamin C, the dual character of NO (either cancerogen or anticancerogen) has greatly been limiting the novel anticancer treatments which administer NO donors. But, lycopene, like quercetin, sulforaphane, kaempferol, myricetin, beta carotene, EGCG and curcumin, can be involved into the anticancer diet without any concern and risk to increase NO which may trigger cancer.

One other anticancer effect of the carotenoid is via the inhibition of GRP78, the chaperon which controls ER with its protein folding capacity, and the inhibition of beta-catenin whose de-regulation is associated with the progress of malignancies since it the deregulation of beta catenin inhibits tumor-suppressor proteins by forming complex with them (Liu et al. 2008; Xu et al. 2015). The inhibition of the chaperon by the flavonoid causes to the damage on protein folding capacity, depolarization of the membrane of ER and subsequently induces the ROS influx while inhibiting the beta-catenin signaling and beta catenin binding to the tumor suppressors which results in the increase of the activity of the tumor suppressors. The mentioned inhibition of GRP78 and beta catenin signaling by the flavonoid may form a synergy for a stronger anticancer effect with the anticancer drugs; sunitinib, sorafenib, SCH727965, metformin and bortezomib combination, tunicamycin, radicicol, KUSs, versipeolstatin, pyrivinium pamoate, tanespimycin and 17-AAG, the anticancer drugs which may synergistically inhibit the chaperon with lycopene if a lycopene rich diet is followed during the administration of the mentioned drugs.

Hsp90, the molecular myosin chaperon which is essential for cell division, proliferation and invasion, is inhibited bt the carotenoid (Qui et al. 2013; Palozza et al. 2005). Thus, the anticancer treatments using Hsp90 inhibitors; geldanamycin, 17AAG, tanespimycin, 17-DMAG (geldanamycin analog), 17-AG (17-amino-17-demethoxygeldanamycin; IP-493), trastuzumab, IPI-504, radicicol, AT13387, PU-H71, AICAR(5-aminoimidazole-4-carboxamide-1-β-D-ribofuranoside), herbimycin A, gedunin, celastrol, NVP-AUY922, HSP-990, KU135(novobiocin-derived

C-terminal Hsp90 inhibitor), novobiocin, macbecin, ganetespib, MPC-3100, benzisoxazole Hsp90 inhibitor, 17-GMB-APA-GA, 17-AEP-GA, 17-DMAP-GA, KW-2478, NVP-BEP800, B11B021, nelfinavir mesylate, VER-50589 and VER-49009, honokiol and also cytarabine, carboplatinum, toptecan, vincristine, cyclophosphomide, cisplatin, methotrexate and etoposide, may show stronger anticancer potential when lycopene rich foods are consumed heavily during the administration of one or some of the mentioned Hsp90 inhibitors.

Lycopene is among the bio-active compounds; curcumin, green tea, 3,3'-diindolymethane resveratrol and vitamin D which attenuate cancer inducing signallings; Hedgehog and Wnt (Sarkar et al. 2010). Therefore, the involvement of lycopene and lycopene rich foods into the anticancer diet, may form a synergy with the following Hedgehog inhibitors; SANT1-SANT4, CUR-61414, HhAntag-691, GDC-0449, saridegib, phthaladines, mukul, guggulsterone, itraconazole, NVP-LDE225, TAK-441, XL-139, HTS piperidines, MRT-92, MRT-83, PF-04449913, N-acylethanolamides, endocannabionids, IPI926, BMS-833923, LEQ506, GANT61, ribotnikinin, HPI1-4, 2-acylglycerols and 2-alkylglycerol.

Another signaling which is often concerned in anticancer treatments, Wnt signaling, the signaling as one of the essentials for embryonic development cell migration and cell proliferation. The association between the signaling and the progress of various cancers, has been informed by the studies; Plakis 2012; Anastas and Moon 2013; Reya and Clevers 2005; Klaus and Birchmeier 2008. The important detail here is the close link between Wnt signaling and beta catenin, the protein, whose deregulation leads to cancer because normally, the protein inhibits tumor-suppressor proteins by making complex with them. The mutations in Beta catenin and also APC (Adenomatous polyposis coli), the negative regulators of B-catenin, were found to be dependent on Wnt signaling (Voloshanenko et al. 2013).The inhibitory effect of the carotenoid on Wnt signaling and beta catenin may beneficially effect the anticancer treatments which use Wnt/beta catenin inhibitors; sunitinib, sorafenib, SCH727965, metformin and bortezomib combination, tunicamycin, radicicol, KUSs, versipelostatin, pyrivinium pamoate, tanespimycin and 17-AAG, XAV939, IWR1, IWP-1, IWP-2, JW74, JW55, okadaic acid,

tautomycin, SB239063, ADP-HPD, 2-[4-(4-fluorophenyl)piperazin-1-yl]-6-methylpyrimidin-4(3H)-one, PI34, niclosamide, cambinol, sulindac, 3289-8625, Scaffold A for series of analogs, Scaffold B for series of analogs, JO1-017a, NSC668036, Flipin, IC261, PF670462, bosutinib, PHA665752, imatinib, ICG-001, ethacrynic acid, ethacyrnic acid derivative, PKF115-584, PNU-74654, PKF118-744, C6P049090, PKF118-310, ZTM000990, BC21, GDC-0941 and Rp-8-Br-cAMP (Voronkov and Krauss 2012). Also, sorafenib (Xiao et al. 2011), RING finger protein43 (RNF43) (Koo et al. 2015), tetrandrine (He et al. 2011), geldanamycin (Wang et al. 2007), FH535 (Singh and Katiyar 2013), fulvestrant (Wang et al. 2014), vorinostat (Galimberti et al. 2009), curcumin (He et al. 2014), quercetin (Mojsin et al. 2014), resveratrol (Hope et al. 2008; Ji et al. 2013), apigenin (Liu et al. 2015), folate (Han et al. 2009), kaempferol, isohamnetin, genistein, baicalein (Park and Choi 2010), EGCG (Oh et al. 2014), sulforaphane (Li et al. 2010) inhibit Wnt/beta-catenin signaling. So, the lycopene rich foods; tomatoe, red carrot, gac, papaya, watermelon, guava, pepper, red cabbage, asparagus and mango, may enhance the mentioned anticancer drugs and bioactive compounds by creating a synergy via the inhibition of wnt/β-catenin signaling. On the other hand, the effect of beta carotene, I3C and ascorbic acid on Wnt/β-catenin signaling is still unknown and needs to be highlighted with the studies in near future.

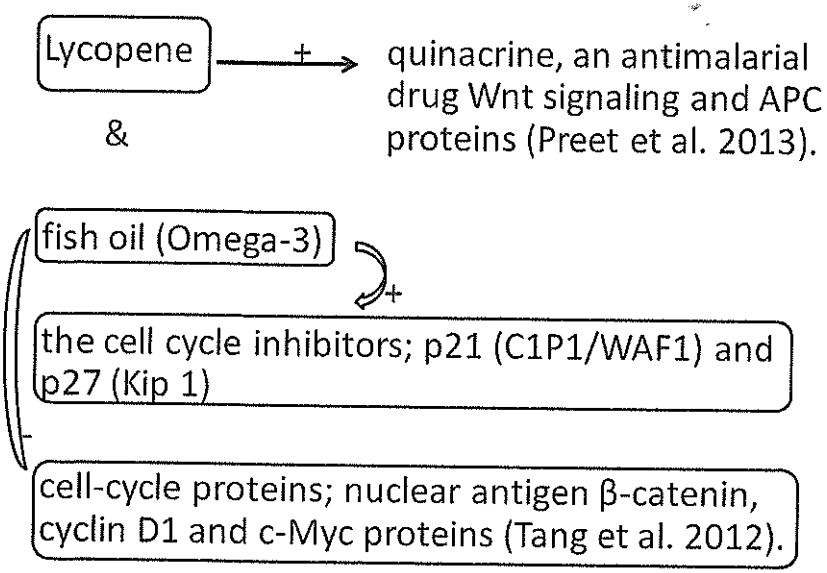


FIGURE 68

The carotenoid synergistically increases quinacrine, an antimalarial drug which has gained a common use with its anticancer effect, by inhibiting both Wnt signaling and APC proteins (Preet et al. 2013). Besides, lycopene as combined with fish oil, augments the expression of the cell cycle inhibitors; p21 (C1P1/WAF1) and p27 (Kip 1), while it also suppresses the proteins; proliferating cell nuclear antigen β-catenin, cyclin D1 and c-Myc proteins, the proteins all of which trigger cell proliferation (Tang et al. 2012).

The other anticancer effect of the carotenoid may be due to its inducing effect on the tumor suppressor gene and apoptotic protein BRCA1 (Nakanishi et al. 2015). The apoptotic protein shows its anticancer effect by reducing the expression of cyclin B1 (the regulatory protein involved in mitosis), while inducing the other apoptotic genes GADD45 and GADD153 (the growth Arrest and DNA Damage 45 and 153, the genes which modulate tumor formation, arresting the growth of cells while damaging DNA) (MacLachlan et al. 2000). An important detail here is the very low doses of I3C (20 μM) and genisten (0.5-1.0 μM) are sufficient to induce BRCA1 (Fan et al. 2006; Teodoro et al.

2012). Since indol-3-carbinol, resveratrol and sulforaphane are the other bio-active compounds that induce BRCA1 as previously mentioned in the part related to genistein, a mix-diet from lycopene, I3C, resveratrol, sulforaphane and genistein, may be useful in anticancer treatments. But, unfortunately, the association of many of the anticancer drugs with BRCA1 still requires to be highlighted.

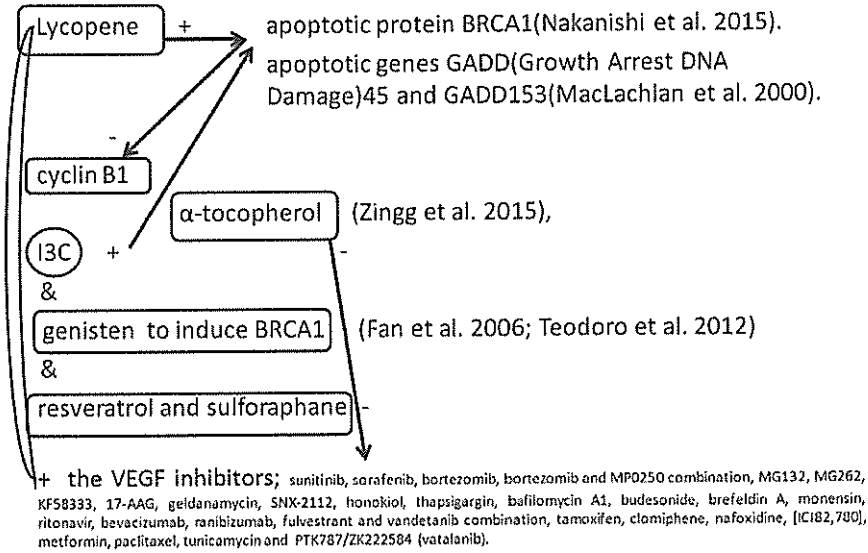


FIGURE 69

Lycopene also inhibits VEGF, the Vascular Endothelial Growth Factor, which is the signal protein to stimulate vasculogenesis, the process of blood vessel formation and angiogenesis (Yang et al. 2011; Huang et al. 2008). The mentioned inhibitory effect of the carotenoid on VEGF, may enhance the anticancer potential of the VEGF inhibitors; sunitinib, sorafenib, bortezomib, bortezomib and MP0250 combination, MG132, MG262, KF58333, 17-AAG, geldanamycin, SNX-2112, honokiol, thapsigargin, bafilomycin A1, budesonide, brefeldin A, monensin, ritonavir, bevacizumab, ranibizumab, fulvestrant and vandetanib combination, tamoxifen, clomiphene, nafoxidine, [ICI82,780], metformin, paclitaxel, tunicamycin and PTK787/ZK222584 (vatalanib). So, the involvement of the lycopene rich foods; tomatoe, red carrot, gac,

papaya, watermelon, guava, pepper, red cabbage, asparagus and mango, during the treatment with VEGF inhibitors may be beneficial, creating a synergy to inhibit VEGF.

Lycopene's one other anticancer effect may be due to its inhibitory effect on ERK (the serine/threonine kinases which produce anti-apoptotic signals) (Feng et al. 2010; Chan et al. 2009). As a result, the anticancer drugs and bio-active compounds/foods that inhibit ERK; quercetin and quercetin rich foods; caper, onion, cocoa and cocoa powder, cranberries, berries, kale, green tea, black tea, lettuce, asparagus and green pepper, emetine, fluorosalan, lestaurtinib, ectinascidin 743, chromomycin A3, bortezomib, vitamin C and vitamin C rich foods, genistein and genistein rich foods, e. g. kudzu, soybean, favabean, lupine, psorolea, miso, banana, broccoli, fresh cabbage, grapefruit, fresh spinach, tomato, lettuce, citrose fruits, sulforaphane and sulforaphane rich foods, e.g.broccoli, fresh cabbage, radish, mustard, Brussels sprouts, cauliflower, Chinese kale, turnip, vorinostat, lapatinib, fulvestrant, PD98059, UO126, honokiol, may benefit from the involvement of the lycopene rich foods into the diet, creating a synergy via the inhibition of ERK. On the other hand, the inhibition of the anti-apoptotic proteins; Bcl-2, Bcl-l, Bax-l (these proteins are anti-apoptotic in cancer cells while they are apoptotic in healthy individuals, depending on various conditions which still remains unknown) (Liu et al. 2006; Soares et al. 2014) by lycopene, may enhance the anticancer potential of the anticancer drugs; HA14-1, AT-101, obatoclax, ABT-263, ABT-737, sunitinib, sorafenib, thapsigargin, bortezomib, 17-AAG, vorinostat, honokiol, metformin, tetrandrine, tamoxifen, geldanamycin, radicicol and raloxifen, creating a synergy via the inhibition of Bcl proteins.

An important finding about the anticancer potential of the carotenoid is the prevention from the smoke-induced changes in p53 and p53 phosphorylation (Liu et al. 2006). The finding does not only reveal a possible benefit of combined use of lycopene or lycopene rich diet with mutant p53 inhibitors (e.g. suberoylanilide hydroxamic acid, panobinostat, PCI-24781, luteolin, EGCG, CP-31398, YK-3-237, trichostatin A, chidamide, LAQ824, sirtinol, salermide, FR901228, AICAR, NSC59984, tubacin and N-2, but also indicates to its anticancer effect against smoking.

THE STUDIES as RELATED to the ASSOCIATION of LEUCOPENE and VARIOUS TYPES of CANCER

- 508 breast cancer/505 control/9.9 years of follow up/≥45 years of age/ alcohol adjusted, smoking adjusted/9.9 years of follow-up/16.741 μg/d(as the highest quartile of lycopene intake (1.06, 0.81-1.37, 95% CI) versus 3.32 μg/d (as the lowest quartile) (R:1.00, 95% CI) did not make any change (Sesso et al. 2005).
- 47365 men/2481 men with prostate cancer/1986-1992/smoking adjusted, alcohol adjusted/40-75 years of age/≥2 servings/ week tomato consumption (0.66,0.47-0.93, 95% CI) versus <1 serving/month (R:1.00, 95 CI) decreased the risk of prostate cancer (Giovannucci et al. 2002).
- 23631 men and women/55-74 years of age/smoking adjusted, alcohol adjusted/ alcohol4.2 years of follow up/1338 with prostate, lung, colorectal and ovarium cancer/>3 servings/week raw tomato (1.04, 0.86-1.27, 95% CI) versus <2.5 servings/ month (R:1.00, 95 % CI) decreased the risk (Kirsh et al. 2006).
- 132 cancer free control/65 men with prostate cancer/smoking adjusted, alcohol adjusted/1993-1997/<60-70≤years of age/0.40 μmol/L plasma lycopene level (0.17, 0.04-0.78, 95% CI) versus 0.17 μmol/L (R:1.00, 95% CI) decreased the risk (Lu et al. 2001).
- 41837 women with lung cancer/2814 control/ 4 years of follow up/55-69 years of age/ smoking adjusted, alcohol adjusted/≥5 servings of lycopene rich foods (1.21, 0.91-2.53, 95% CI) versus ≤1 serving of lycopene did not make any change(Steinmetz et al. 1993)/Case study.
- 86402 men/10.864 men with prostate cancer/1992-1997/ <65-85≥85 years of age/smoking adjusted, alcohol not/6.1-30.3 mg/d (1.02, 0.69-1.49, 95% CI) versus <2.8 mg/d /R:1.00, 95% CI) did nat make any change (Wang et al. 2016).
- 58.279 men/642 men with prostate cancer/6.3 years of follow-up/55-69 years of age/ alcohol adjusted, smoking not/2

mg/d lycopene intake (1.03, 0.76-1.40, 95% CI) versus 0.1 mg/d (R:1.00, 95% CI) did not make any effect on the risk of prostate cancer (Schuurman et al. 2002).

- 259 men and women/1991-1998/smoking adjusted/61 deaths from oral, pharynx and larynx cancers/ alcohol adjusted/280 µg/L plasma lycopene concentration(0.53,0.30-0.93, 95% CI) versus <270 µg/L(R:1.00, 95% CI) decreased the risk (Mayne et al. 2004).
- 34198 adventists/61 lung cancer/1977-1982/25-80≤years of age/ smoking adjusted, alcohol not/≥7 times tomato/week (0.65, 0.29-1.47, 95% CI) versus<3 times tomato/week (R:1.00, 95% CI) decreased the risk of lung cancer (Fraser et al. 1991).

The main problem about the current data as related to the 'cancer and lycopene' association, by considering the mentioned cohorts above, two barriers seem to be exist to determine the lycopene's anticancerogenic effect. First, the number of cohorts, like many other anticancer cohorts, is too insufficient to be able to highlight the anticancer of lycopene though there are some important findings of some of the cohorts that indicate to its protective effect on some types of cancer. Second and the more important one is that, an important number of the cohorts use tomatoe or carotenoids, assuming them as the indicators of lycopene though they are not since tomato is not only rich in lycopene (19.7±1.00-20.6±1.8 mg/Kg) but also a great source of zinc (6.2±0.1-8.0±0.3 mg/Kg) and B-carotene (0.23-2.83 mg/100 g) while it has also a high content of total phenolic content (35.05±0.44-557.8±10.2 mg/Kg), all of which can show anticancer effect like lycopene (Nour et al. 2013; Baranska et al. 2006).

INDOL 3 CARBINOL

One of the most important biochemical of Indol-3-Carbinol (I3C) which protects from cancer, is produced from naturally occurring glucosinolates in a wide variety of plants, especially in cruciferous vegetables in the genus Brassica (e.g., broccoli, cabbage, cauliflower, bok choy and Brussel sprouts (Sarkar and Li 2004). The compound arises from indoyl-methyl glucosinolate when crucifers are crushed or cooked (Beier 1990) which means that it may be useful to chop the vegetable, spread and leave on the kitchen table 15 or 20 minutes to allow the formation of the anticancer substances, glucosinolates and I3C. The ingested I3C can be converted into its biologically active dimer, 3,3'-diindolylmethane (DIM), within the gastrointestinal tract. DIM accumulates in the nucleus and thus, it is highly possible to have contributed to nuclear events that have been attributes to I3C (Kim and Milner 2005). Peroxisome proliferator-activated receptor ϒ (PPAR) is a member of the NHR (nuclear receptor) superfamily, a class of proteins found in certain cells (Lemberger et al. 1996).

Indole-3-carbinol seems to appear as a crucial cornerstone in cancer nutrition since it is a negative regulator of estrogen. I3C causes growth arrest and increased apoptosis and ameliorates the effects of estrogen and thus may prevent particularly the development of estrogen-enhanced cancers including breast, endometrial and cervical cancers. Confirming this, I3C as combined with genistein was determined to induce GADD (Growth Arrest and DNA Damage) expression and thus increase apoptosis while decreasing the expression driven by ER-α, one of the two estrogen receptors (Estrogen receptor alpha) whose activation and overexpression enhance the estrogen activity of estrogen to induce estrogen-enhanced cancers (Giacinti et al. 2006).

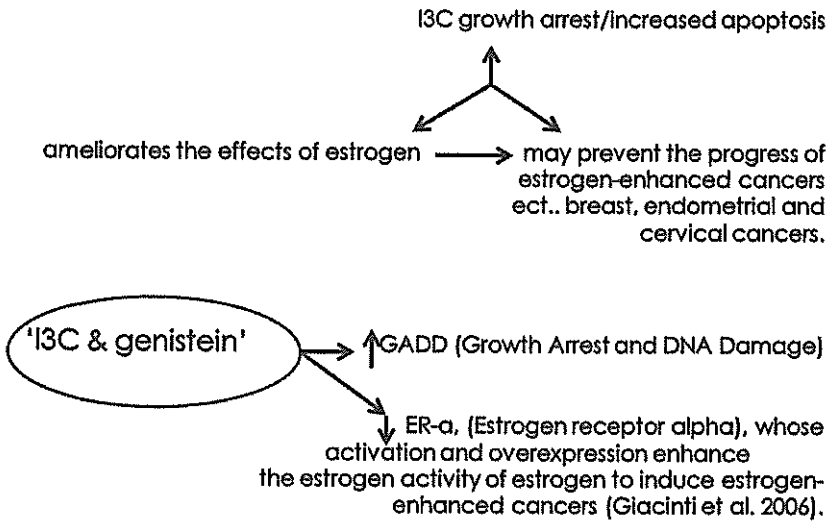


FIGURE 70

Tamoxifen is a nonsteroidal antiestrogen since it is receptor in breast tissue via its active metabolite, 4, hydroxytamoxifen. Tamoxifen works by binding to the estrogen receptor in the breast and other estrogen-sensitive tissues (Cuzick and Baum 1985). The binding of estrogen receptor in breast gained a crucial anticancer status to the drug in the anticancer treatments, especially for breast cancer (Fisher et al. 2005; Powles et al. 2007; Veronesi et al. 2003). In addition to its antiestrogenic effects, tamoxifen also inhibits cell division in cancer cells, like in A549 human lung adenocarcinoma cell line, hep 3B (hepatoma cell line (Jiang et al. 1995), human mast cells (Duffy et al. 2003), within the concentrations ≥ 2 μM (Zheng et al. 2007; Shin and Arteaga 2006) and promotes the production of tumor-fighting white blood cells, the natural killer cells. Confirmingly, the administration of I3C (300 mg/4 weeks and 400 mg/12 weeks) to 70 women, enrolled in a placebo-controlled study, was determined to increase the ratio of 2-hydroxyestrone, while decreasing 16 alpha-hydroxyestrone and inhibiting precancerous lesions of cervix (Wong et al. 1997; Bell et al. 2000; Terry et al. 2001). Tamoxifen and I3C may be in synergism since both act as antiestrogen which should be taken into consideration in the anticancer treatments.

The combined administration of I3C and tamoxifen may a much greater yield, especially in the treatments of estrogen related cancers.

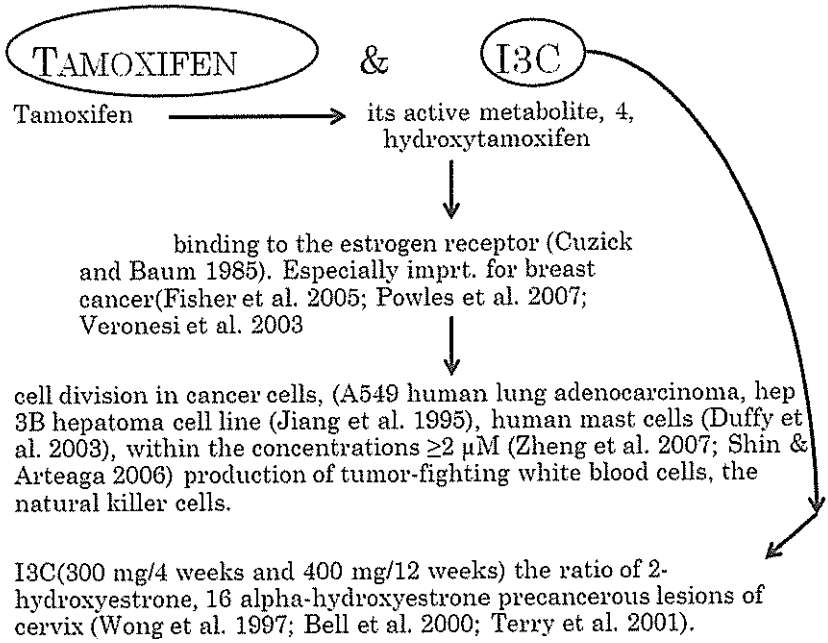


FIGURE 71

The anticancer effects of indols including I3C and isothiocyanates due to their triggering effect on phase 2 enzymes, while inhibiting phase 1 enzyme activity, is the main attribute of Brassica vegetables which makes vegetables as crucial in cancer nutrition (van Poppel et al. 1999). 17β-estradiol, the predominant circulating ovarian steroid which is the main cancerogen in breast cancer, causes to the loss of chromosome 4, deletions in chromosomes 3p12.3-13, 8p11.1-21, 9p21-qter and gains in 1p, and 5q15-qter in MCF-10F (breast cancer cell line) (Russo et al. 2006). I3C has been found to inhibit 17β-estradiol (Weng et al. 2008; Marconett et al. 2011). The two metabolic products of I3C, diindolymethane (DIM) and indolylcarbazole (ICZ), seem to have the most attention as active constituents in I3C, while both are decomposed and absorbed by digestion track, using enzyme activity and stomach acid, which is the main reason for the higher bioavailability of I3C when taken orally

as compared with its intravenous or intraperitoneal administrations (Brignall 2001). The two constituents induce the cytochrome p450 isoenzymes; CYP1A1 and CYP1A2, whose aryl hydrocarbon receptors (AhR) activates phase I and II metabolizing enzymes, while AhR is involved in various cell signaling pathways in cell cycle regulation and normal hemostasis. Additionally, the isoenzymes play an important role in the detoxification of environmental carcinogens as well as the metabolic activation of dietary compounds with cancer preventive activity (Androutsopoulos et al. 2009).

A group of chemicals; aniline dyes (a toxic organic compound with a phenyl group attached to an amino group, used for rubber processing chemicals, herbicides, dyes and pigments (Kahl et al. 2007), 2-Naphthylamine, the aromatic amine in cigarette smoke, 4-Aminobiphenyl, which is used to manufacture azo dyes, X enylamine which is an antiviral, benzidine and O-toluidine, the organic aromatic amine compounds which are used in the production of dye, all of which are called as arylamines(any of a group of amines in which one or more of the hydrogen atoms of ammonia are replaced by aromatic groups) have long been concerned as cancerogens in cigarette smoke and industry, especially leading to bladder cancer (Carreon et al. 2014; Bulbulyan et al. 1995; Vineis and Pirastu 1997; You et al. 1990). NAT2, N-acetyltransferase 2 (arylamine N-acetyltransferase), is the other enzyme which is similar to the enzymes CYP1A1 and CYP1A2, works in synergism with them, catalyzing the detoxification of the mentioned cancerogen arylamines (Seow et al. 2001). Thus, I3C, via the activation of CYP1A1 and CYP1A2 as in synergism with NAT2, can be uselful to prevent smoking related cancers.

The aryl hydrocarbon receptor (AhR), a legand-dependent transcription factor that regulates the transcription of certain key enzymes like; CYP1A1, CYP1A2 or NAT2 which are involved in the metabolism of xenobiotic substances including some drugs, interacts with a number of hormones like estrogen. Thus, the activation of the AhR may serve as a target for breast cancer therapy. Polymorphism in the AhR or the enzymes; NAT2, CYP1A2 and CYP1A1 regulated by the AhR, may cause variations in response to certain drugs (Ramadoss et al. 2005). AhR activation by I3C has also been found to alter the

expression of estrogen receptor alpha (ERα) whose ratio to ERβ correlates positively with enhanced cellular proliferation (Marconett et al. 2010).

2-hydroxyestrone and 2-hydroxyestradiol makes protection against the estrogen-agonist cancerogen effects of another estrogen metabolite, 16α-hydroxyestrone formation and thus, acts as anticancerogen in breast cancer (Lord et al. 2002). The cruciferous vegetables and indole-3-carbinol and its active form, diindolymethane (DIM), may induce the catalysis of 2-hydroxyestrone by CYP1A1 and therefore I3C and its rich sources like cruciferous vegetables may appear to be affective dietary means for reducing the risk of breast cancer via I3C, CYP1A1 and 2-hydroxyestrone. On the other hand, the polymorphisms in CYP1A1, CYP1A2 and NAT2, like the heterozygous Ile/Val genotype in CYP1A1/A2, variant allele 462Val and 6235C carriers, T-C transversion at nucleotide position 3801, MspI, Ile462Val, T3205C and Thr461Asn contribute to the progress of breast cancer, metastasis of lymph nodes and lung cancer (Surekha et al. 2009; Miyoshi et al. 2002; Wang and Wang 2013; Jose et al. 2010). Thus, the protection of CYP1A1/A2 and NAT2 from polymorphisms and their correct expressions are extremely important to allow binding of 16α-hydroxyestrone and detoxification of arylamines, all of which contribute to the decrease in the risk especially lung and breast cancers. On the other hand, indol-3-carbinol appears as an important inducer of CYP1A1/1A2 which convert estrogens of 2-hydroxyestrones (2-OHO) that undergo methylation to produce the protective 2-methoxyoestrogens (2-MeO). 2-methoxyoestrogen has been found to have anti-proliferative actions in phase 1 and 2 trials for the treatments of refractory breast cancer (Mueck and Seeger 2007). On the other hand, 300-400 mg supplementation of I3C/month, was informed as increasing the 2:16-OHO ratio during breast cancer (Reed et al. 2005).

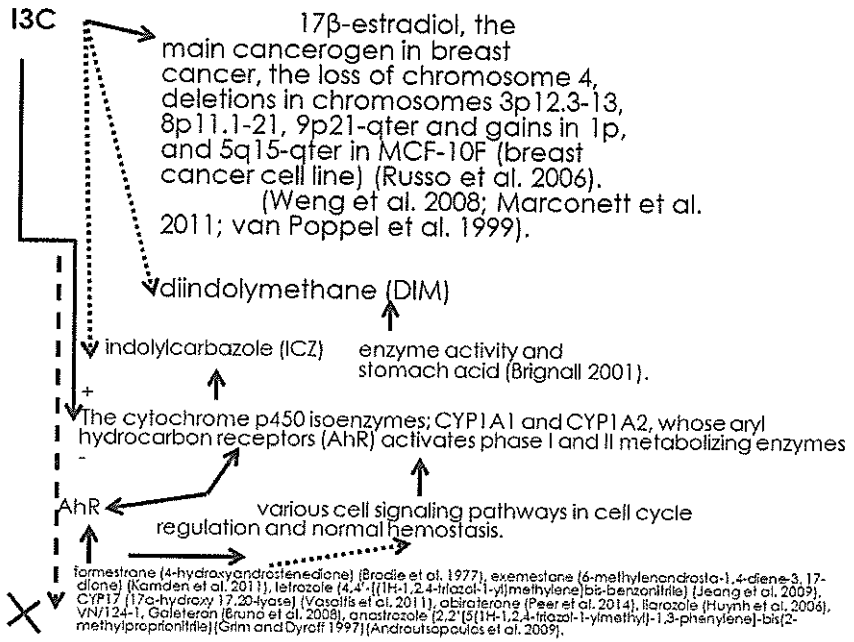


FIGURE 72

The I3C-dependent activation of the aryl hydrocarbon receptor, AhR, initiates Rbx-1E3 ligase (a complex protein that recruits a ubiquitin, small protein, conjugating enzyme) mediated ubiquitination (conjugation of small proteins) and proteasomal degradation of ERalpha protein. On the other hand, the binding of GATA-3, trans-acting T-cell-specific transcription factor a protein which regulates luminal epithelial cell differentiation in the mammary gland, with ERalpha, is inhibited by I3C and this disrupts GATA3 interactions with ERalpha which results in a loss of GATA 3 and ERalpha expression. The ectopic expression of GATA3 prevents the inhibition of ERalpha by I3C, but prevents the inhibition of ERalpha by I3C, but the loss in the expression of GATA3 allows to a greater inhibition of ERalpha by I3C. Briefly, one of the anticancer effects of I3C is via the GATA3 expression besides the inhibition of ERalpha expression (Marconett et al. 2010).

2,3,7,8 TCDD tetrachlorodibenzo(p)dioxin (TCDD), a cancerogen formed as a result of organic materials, binds AhR to COX-2, leading to the activation of COX-2, the enzyme which induces angiogenesis, cancer

and inflammation. DIM(diindolylmethane) and also RES (resveratrol) have been informed to reduce the TCDD- induced-binding of AhR, alleviating the activity of COX-2 (Degner et al. 2009).

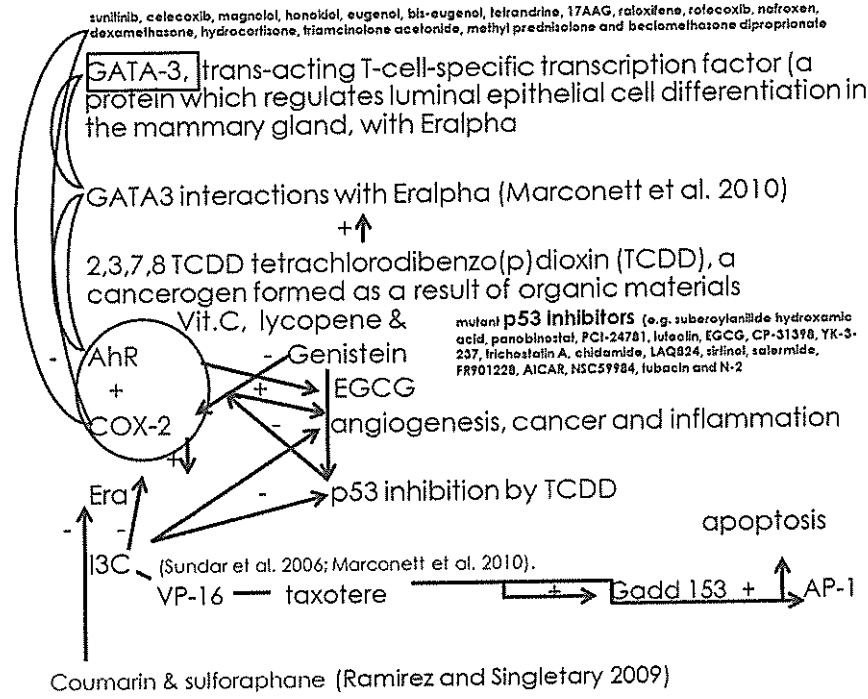


FIGURE 73

Fenretinide (4-hydroxyphenylretinamide; 4HR) (INN) is one of the anticancer drug substances, a synthetic retinoid derivative of vitamin A. Fenretinite causes ceramide (a wax-like substance) to build up in tumor cells and kills tumor cells by using reactive oxygen species (ROS), resulting in apoptosis, like many other anticancer drugs (Wu et al. 2001; Franca et al. 1993; Anita et al. 2003). The activity of p53 protein, which is one of the tumor suppressors is inhibited by an AhR ligand, 2,3,7,8-Tetrachlorodibenzo-p-dioxin, TCDD via the phosphorylation or acetylation of p53 by TCDD. The inhibition of p53 by TCDD leads to the activation in breast and also liver (Ambolet-Camoit et al. 2010; Seifert et al. 2009). The activation of ERα which acts as tumor iniator as a result of p53 inhibition by TCDD, has been confirmed to be inhibited

by I3C which appears as one of the inhibitors of ERα, degrading the protein and activating AhR, p53 (Sundar et al. 2006; Marconett et al. 2010). BRCA1 and BRCA2 are the human genes that produce tumor suppressor proteins. They help repair the damage in DNA, ensuring the stability of the cell's genetic material. The mutations of both genes account for 20 to 25 % of hereditary breast cancers and 5 to 10 % of all breast cancers (Easton 1999; Campeau et al. 2008). The BRCA1 and BRCA2 genes contain unusually high densities of repetitive elements and thus, the aromatic alterations of the genes are driven by rearrangements between the repetitive elements. The mentioned tendency of the genes to the somatic alterations appears as one of the reasons for especially breast and ovary cancers (Welcsh and King 2001). But, I3C can protect the tumor suppressor genes; BRCA1 and BRCA2 against such alterations while I3C induces BRCA1 expression and both I3C and BRCA1 inhibit estrogen (E2)-stimulated estrogen receptor (ERalpha) activity in both breast (MCF-7 and T47D) and prostate (DU-145 and LNCaP) cancer cells (Fan et al. 2006). On the other hand, fenretinide which acts as antiproliferative at a concentration of 1 μM in humans (Veronesi et al. 1999), may show more anticancer potential in cancer treatments if administered as combined with I3C by protecting and inducing BRCA1 or BRCA2 (Veronesi and Decensi 2001) since both I3C and Fenretinide induce the tumor suppressors; BRCA1 and BRCA2 which needs further studies to be confirmed and concerned as a noıvel application in cancer treatments. Another important reason for the possibility of the stronger antiproliferative effect of such combined administration, may be the generation of reactive oxygen species by both I3C and Fenretinide, increasing the amount of reactive oxygen species to kill tumor cells (Hwang et al. 2011; Shimamoto et al. 2011; Bai et al. 2013). Polycyclic aromatic hydrocarbons such as benza[a] pyrene, the carcinogenic and mutagenic hydrocarbons, the carcinogenic and mutagenic hydrocarbons from uncooked, cured and processed food may contaminate the consumer most with cereals and vegetables rather than meat, except the heavy consumption of meat cooked over an open flame, above ≥100 C (Phillips 1999).

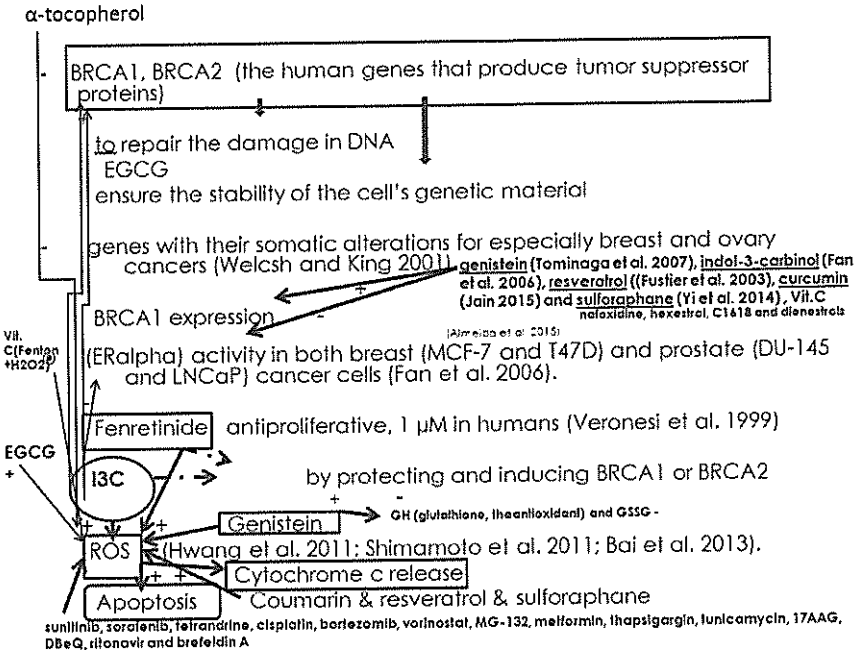


FIGURE 74

CYP1A1 and CYP1A2, like I3C cause the generation and induction of reactive oxygen species, followed by their production of cancerogen reactive intermediates from polycyclic aromatic hydrocarbons (PAHs) and heterocyclic aromatic amineslamides (HAAs) (Ma and Lu 2007). Heterocyclic aromatic amines, namely the aminoimidazoazaarene (AIAs) compounds and the aminopyridoindoles, contaminate the consumer especially with the consumption of grilled rich protein sources like grilled fish, grilled beef and even cooked grain products (Robbana-Barnat et al. 1996).

In spite of their polycyclic aromatic hydrocarbons in their cooked forms, the cruciferous vegetables with their I3C rich content, may form an antiproliferative effect during cancer by generating and inducing reactive oxygen species, triggering the activity of CYP1A1 and CYP1A2 to increase ROS and their killing potential on tumor cells, while triggering the activity of tumor suppressors; BRCA1 and BRCA2. Thus, cruciferous vegetable consumption alone or as combined with the

treatment administering Fenretinede, should carefully be concerned in cancer nutrition.

DNA damage-inducible gene 153, Gadd 153 gene, is one of the growth arrest and DNA damage inducible genes which is important in signal transduction pathways in response to DNA damage. The induction of the gene could modulate the sensitivity to anticancer agents in association with apoptosis like the apoptosis followed by the introduction of the gene into MKN45 gastric cancer cells following the treatments of VP-16 and taxotere, activating AP-1-associated signal transduction pathways that leads to apoptosis (Kim et al. 1999). On the other hand, there is a synergism between I3c and Gadd 153 (Auborn 2003).

GRP78, also called as Binding immunoglobulin protein, BIP, is a central regulator of endoplasmic reticulum (ER) function because of its protein folding capacity which means that it is a chaperon. It is a 78kDa glucose-regulated protein, encoded by HSPA5 gene. The chaperone is located in the lumen of the endoplasmic reticulum (ER) that binds newly synthesized proteins as they are translocated into endoplasmic reticulum. The protein targets misfolded proteins for degradation, ER Ca(2+)-binding and controlling the activation of transmembrane ER stress sensors. Especially, the lower oxygen concentrations in tumors induce GRP78 expression on the cell surface of cancer cells (Li and Lee 2006) which leads to the development of new approaches against cancer. Binding of activated alpha2-macroglobulin, which is a multifunctional binding protein with protease and cytokine scavenging properties whose concentrations are higher in cancer cells, contributes to metastasis (Smorenburg et al. 1996), to cell surface. The triggering effect of activated alpha2 macroglobulin on GRP78 activates Akt, the protein that modulates the function of numerous substrates, involved in the regulation of cell survival and cellular growth (Fresno Vara et al. 2004), leading to cell proliferation and cancer. GRP78 and cancer associations were also claimed in various cases (Lee 2007; Delie et al. 2012; Su et al. 2010; Li et al. 2013). On the other hand, I3C induces the activity of GRP78, increasing the severity of invasion and tumor progress (Lu et al. 2012; Galluzzi et al. 2012; Ye et al. 2015 and Sun et al. 2004). But, HKH40A, WMC79 (the synthetic agent with potent activity

against colon and hematopoietic tumors) and the 8-methoxy analog of it, Epirubicin, show anticancer effect by targeting and reducing the activity level of GRP89 (Kosakowska-Cholody et al. 2014; Chang et al. 2012). In the consideration of tamoxifen, I3C or I3C rich food consumption may be suggested since the drug is claimed not to make any effect on GRP78 levels (Jagtap et al. 2015). Similarly, another important point as regarded to I3C supplementation or I3C food consumption and treatment by anticancer drug appears about taxane and vinblastine. Although, both chemotherapeutic drugs gained a wide use in cancer treatments, resistance to these agents is frequently encountered. Taxol and vinblastine induce multiple arms of the Endoplasmic Reticulum (ER) stress response, including up-regulation of glucose-regulated protein 78 (GRP78) expression which is the main target used for the anticancer action of both agents. Abrogation of GRP78 induction sensitizes breast cancer cells to these agents. Treatment with (-)-epigallocatechin gallate (EGCG), a GRP78 inhibitor, synergistically promotes taxol-and vinblastine-induced cell death. Therefore, it seems vitally important that I3C supplementation or I3C rich foods such as cruciferous ones should be avoided during the chemotherapeutic treatments with taxol and/or vinblastine since I3C induces GRP78 activity as being contraindicated with both agents, while tea, rich in EGCG, may be advised.

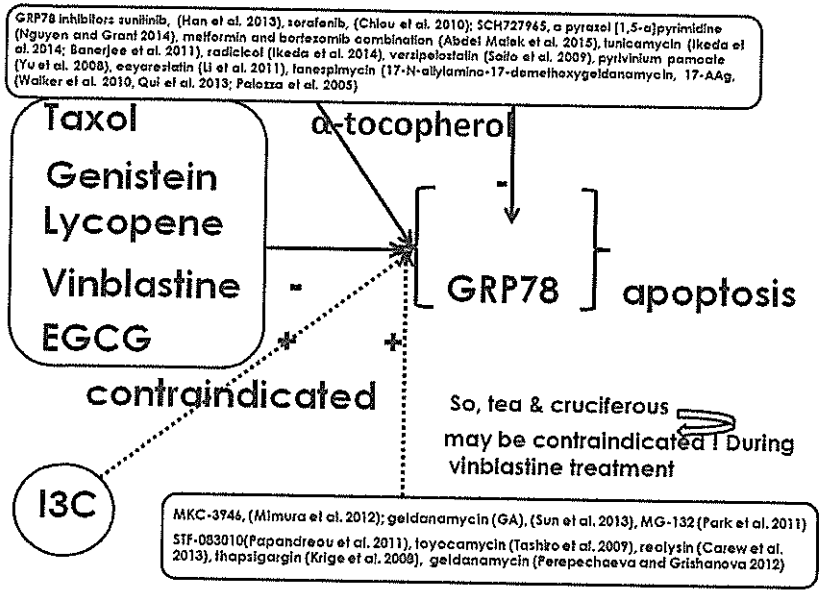


FIGURE 75

The other GRP78 inhibitors among anticancer drugs; sunitinib, the antiangiogenic drug especially used in the treatment of renal cell carcinoma (Han et al. 2013), sorafenib, a newly established anticancer drug, found to be effective in systemic treatment for advanced hepatocellular carcinoma (Chiou et al. 2010); SCH727965, a pyrazol [1,5-a]pyrimidine with a potential antineoplastic activity (Nguyen and Grant 2014), metformin (an oral antidiabetic drug) and bortezomib combination (Abdel Malek et al. 2015), tunicamycin, a glucosamine-containing pyrimidine nucleoside and an antibiotic (Ikeda et al. 2014; Banerjee et al. 2011), radicicol (also known KUSs (the novel VCP modulators and ATPase inhibitors) (Ikeda et al. 2014), versipelostatin (a natural product derived from a bacterium) (Saito et al. 2009), pyrivinium pamoate (Yu et al. 2008), eeyarestatin (Li et al. 2011), tanespimycin (17-N-allylamino-17-demethoxygeldanamycin, 17-AAg, a derivative of the antibiotic geldanamycin) which has currently been studied in the treatment of cancer (Walker et al. 2010), may be contraindicated with I3C supplementation or I3C rich food consumption, since I3C induces GRP78 expression and increases its activity, increasing the resistance

of cancer cells to the mentioned GRP78 inhibitors. On the other hand, the anticancer drugs which induce GRP78 or have no any clear effect on it, namely; MKC-3946, an endoplasmic reticulum to nucleus signaling 1 alpha ribonuclease domain inhibitor (Mimura et al. 2012); geldanamycin (GA), a naturally occurring benzoquinoid ansamycin antibiotic with a potent antitumor activity (Sun et al. 2013), MG-132, a proteasome inhibitor which blocks the action of proteasomes that break down anticancer proteins like p53 (Park et al. 2011), STF-083010, a small-molecule inhibitor of Irel (serine/threonine-protein jkinase) (Papandreou et al. 2011), toyocamycin (Tashiro et al. 2009), reolysin, an antiviral against reoviruses while triggering heavy proteins of viral products leading to endoplasmic reticulum stress whch causes apoptosis (Carew et al. 2013), thapsigargin which targets peptide containing aspartic acid with antineoplastic activity (Krige et al. 2008), may also be contraindicated with I3C. Because they do not show any inhibitory effect on GRP78 or some of them even induce GRP78 activity or expression, this attribute of them may be encountered as one of the important side effects of this later group. Any I3C supplementation or I3C rich food consumption during the administration of one of the drugs in this group may trigger the expression or the activity of GRP78 much more, increasing the resistance of tumor cells to any of the anticancer drugs.

CYP1A1 cytochrome P450-1A1, the extrahepatic phase I metabolizing enzyme, is enhanced by aromatic hydrocarbon or aryl hydrocarbons which are derived from an aromatic ring, like configuration of six carbon atoms in aromatic compounds which is known as 'benzene' and exists in monocyclic or polycyclic forms. The polycyclic hydrocarbons are claimed as one of the initial carcinogens in various cancers, especially lung, breast, larynx and bladder cancers (Mastrangelo et al. 1996; Gammon et al. 2002; Zhang et al. 2009; Wagner et al. 2014). They are metabolically activated in cells by cytochrome P450 enzymes including CYP1A1/-A2 and/or peroxidases to reactive intermediates that damage DNA, like the binding of dihydrodiol epoxides to exocyclic amino groups of purines to DNA or binding to the N7 or C8 of purines to form unstable adducts that depurinate to leave apurinic sites in DNA (Melendez-Colon et al. 1999). These chemicals are formed especially when muscle meat including beef, pork, fish or poultry is cooked using

high temperature methods like pan frying of grilling over an open flame (Cross and Sinha 2004). The heat treatments which have cancerogenic potential due to their PAH production capability are as follows, orderly; ≤100 °C<(+300)-(+500) °C<(+600)-(+1000)<≥(+1000 °C) (Pakpahan et al. 2009). The meat type, cooking method and the level of heat determine the amount of PAH production. It especially begins above 148 °C (300 F), accompanied by smoke or charring which contribute significantly to PAH production (Jagerstad and Skog 2005). It seems greatly abnormal and unacceptable that vegetables, fruits, cereals and legumes, briefly plant origin foods, still continue to be blamed as cancerogens because of their higher fructose contents though these foods can only be contaminated with one of the mentioned important cancerogens, like PAHs, and can only be accidentally and naturally contaminated by the means of atmosphere or soil, while the muscle meat and its products can directly be contaminated by overcooking (not naturally or accidentally, but intentionally, in an organized manner, with culinary purposes to increase sensory quality of the meat dishes!!), like grilling and smoking, that are applied to the plant origin foods very rarely!. The most important point here is that, I3C has been informed to induce the activity of CYP1A1/-A2 (Yan et al. 2006; Ociepa-Zawal et al. 2007). Thus, the increase in CYP1A1, CYPA2 and CYP3A1 activities, triggered by I3C supplementation or I3C rich food consumption such as the cruciferous ones, as combined with grilled or any overcooked meat, fish, poultry and their products, may increase the cancerogenic intermediates produced by the induced CYP1A1, CYP1B1 or CYP3A1 by I3C, leading to DNA damage and hence, increasing the risk of cancer in persons without cancer, but also worsening the prognose of the treatment during cancer.

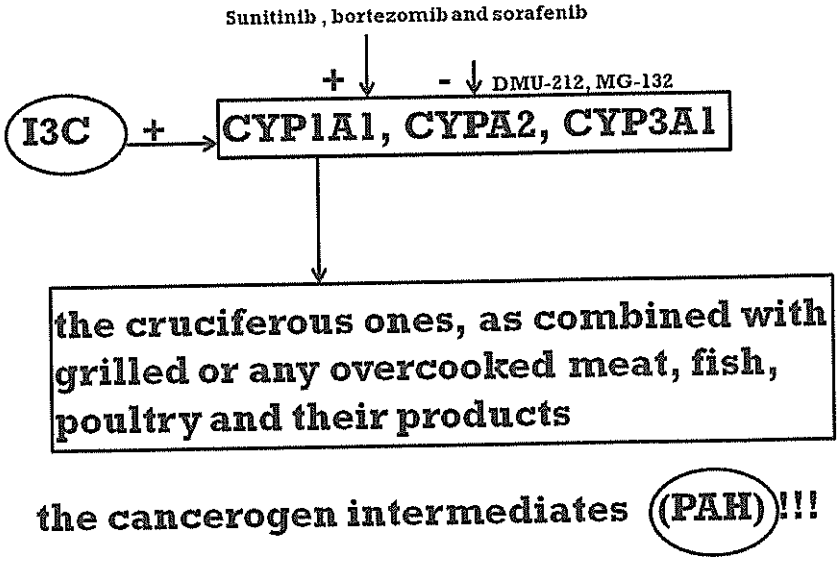


FIGURE 76

Sunitinib and sorafenib induce p450 cytochroms, namely; CYP1A1 (Maayah et al. 2013; Bullock et al. 1995; van Erp et al. 2009; Sugiyama et al. 2011; Garcia-Donas et al. 2011; Kim et al. 2013) and I3C and I3C rich foods may be contraindicated and may worsen the prognose during the treatment with the mentioned drugs since they also induce CYP1A1, CYP1B1 or CYP3A1. Note and remember that sunitinib and sorafenib may also be contraindicated with I3C since the drugs treat cancer by inhibiting GRP78 while I3C induces it.

DMU-212, the resveratrol analog (3,4,5,4'-tetramethoxystilbene), inhibits CYP1A1 (Piotrowska et al. 2013), but the detail which is more important is the relation between resveratrol, its synthetic derivative (DMU-212) and CYP1B1, since resveratrol is informed to cause the formation of an important antileukemic agent, piceatannol during its interaction with CYP1B1 (Potter et al. 2002). The dilemma here is the possibility of the increase in anticancer effect in case of the combined consumptions of both I3C and resveratrol rich foods or their supplements during the treatment with DMU-212 that, I3C may increase CYP1B1

expression while DMU-212 may produce more piceatannol from the induced CYP1B1 activity.

Bortezomid, a proteasome inhibitor as one of the anticancer drugs, has been informed to have a higher anticancer potential in the treatment of ovarian cancer after the ovarian cancer cells were sensitized by I3C (Taylor-Harding et al. 2012). This synergism between the drug and I3C, may be due to the CYP1A1 and other P450 enzymes by I3C and as a result, a greater damage on the cancer cells prior to the administration of bortezomid. But, such combination (I3C and bortezomib) may also damage the healthy cells via PAH production. Therefore, I3C supplementation or I3C rich food consumption such as cruciferous vegetables should better be avoided before or during the treatments which administer bortezomid.

MG-132, another proteasome inhibitor, decreases CYP1A1 activity during the cancer treatment with the drug and therefore may be contraindicated with I3C since I3C induces CYP1A1 activity (Anwar-Mohamed et al. 2008).

Geldanamycin, the protein-tyrosine kinase, though decreases CYP1A1, the decrease which causes DNA damage and causes cancer (Perepechaeva and Grishanova 2012), induces the activity of GRP78 which protects ER. Thus, the treatment which administers geldanamycin, may be advised as combined with I3C and I3C rich food consumption since I3C also induces the activity of GRP78.

Cytochrome P450s (CYPs) are a large family of enzymes which catalyze a wide range of reactions from the hydroxylation of alkanes to alcohols, conversion of alkenes to epoxides, arenes to phenols and sulfides to sulfoxides and sulfones. These enzymes have important role in the metabolism of hormones and process of the exogenous molecules like drugs and chemicals. They mediate the metabolic activation of numerous precarcinogens and participate in the inactivation and activation of anticancer drugs. Since some of P450 enzymes are selectively expressed in tumours (Rodriguez-Antona and Ingelman-sundenberg 2006; Murray et al. 1997; Tokizane et al. 2005; McFadyen et al. 2004), especially CYP1B1 may be involved in progression of cancer by altering the tissue response to hormones and clinical response to chemotherapy (Gajjar et al. 2012). Finally, CYP1A1 and 1A2 play

roles in the metabolic aromatic hydrocarbons (PAHs) and heterocycxlic aromatic amines/amides (HAAs) (Ma and Lu 2007).

The inhibition of CYPs, the P450 enzymes, has been an important target in cancer treatment since some of the CYPs were found responsible for the production and activation of some precancerogens while some of them bind hormones to receptors, inducing the cancer progress like in aromatase which binds estrogen to estrogen receptor. The CYP inhibitors as one of today's most common anticancer drugs like tamoxifen, may be contraindicated with I3C because they work by blocking the CYP activity whereas I3C supplementation or I3C rich food consumption, may induce the expression and activity of CYPs. Similarly, the other CYP inhibitors which are administered in breast cancer and post-menapousal period, blocking estrogen binding, namely; formestrane (4-hydroxyandrostenedione) (Brodie et al. 1977), exemestane (6-methylenandrosta-1,4-diene-3, 17-dione) (Kamden et al. 2011), letrozole (4,4'-[(1H-1,2,4-triazol-1-yl)methylene]bis-benzonitrile) (Jeong et al. 2009), CYP17 (17α-hydroxy 17,20-lyase) (Vasaitis et al. 2011), abiraterone (Peer et al. 2014), liarozole (Huynh et al. 2006), VN/124-1, Galeteron (Bruno et al. 2008), anastrozole (2,2'[5(1H-1,2,4-triazol-1-ylmethyl)-1,3-phenylene]-bis(2-methylproprionitrile)(Grim and Dyroff 1997), (briefly the CYP inhibitors that inhibit the key enzymes which catalyzes the biosynthesis of androgens from pregnane precursors, commonly administered in breast and prostate cancers), may be contraindicated with I3C supplementation and I3C rich food consumption because of the same mentioned reason, the triggering effect of I3C on CYP activity and expression. 1,25-D3, a form of vitamin D, which acts as a hormone by binding to a nuclear receptor (the vitamin D receptor) and initiating transcription, has gained attention as a novel anticancer agent because of its ability to inhibit proliferation and induces apoptosis (Gonzales-Sancho et al. 2006; Studzinski et al. 1993). On the other hand, CYP24 catalyzes the hydroxylation at C-24, deactivating 1,25 D3 (Ohyama and Okuda 1991).

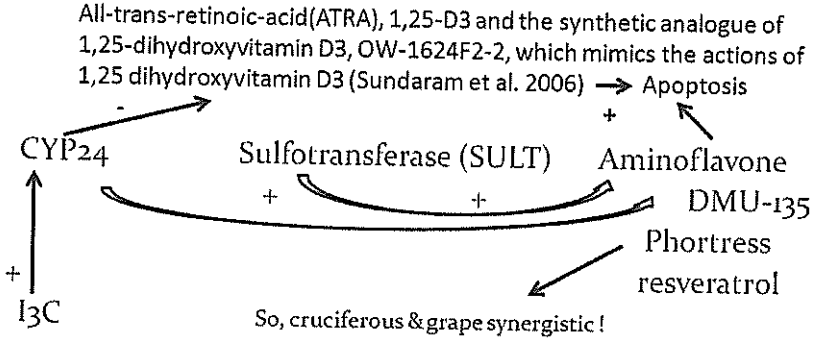
Therefore, the targeting and inhibition of CYP24 may provide the opportunity to increase endogenous levels of 1,25-D3 and thus, the anticancer effect of 1,25-D3 during cancer treatment. For this reason, it seems vitally important that, the I3C supplementation or I3C rich

food consumption, because of its triggering effect on CYPs including CYP24, may be contraindicated with the CYP24 inhibitor, 1,25-D3 and the synthetic analogue of 1,25-dihydroxyvitamin D3, OW-1624F2-2, which mimics the actions of 1,25 dihydroxyvitamin D3 (Sundaram et al. 2006) and the limited number of foods rich in vitamin D, e.g. oily fish (like salmon, mackerel and sardines), cod liver oil, egg yolk, vitamin D fortified milk and dairy products, vitamin D fortified cereals and cereal products, vitamin D fortified orange juice and vitamin D fortified margarine (Holick 2006; Calvo et al. 2004).

The two novel CYP24 inhibitors; VID400 (2-(R)-4-chloro-biphenyl-4-carboxylic acid-(2-imidazol-1-yl-2-phenyl)-ethyl-amide) and SDZ 89-443 (2,2-di-(4-chlorophenyl)-Z-(imidazole-1-yl)-1-(4-chlorobenzoyl-amino)-ethano) (Schuster et al. 2001), may also be contraindicated with I3C induces CYP activation and increases the overexpression of CYPs while the two mentioned CYP inhibitors and others do the opposite.

Another important association besides the association between CYP activity and I3C seems to belong to CYP and retinoic acid. All-trans-retinoic-acid (ATRA), the most active biological metabolite of vitamin A which is being used for the treatments and prevention of several types of cancer (Miller 1998; Njar et al. 2006), has gained a limited application platform in cancer treatments since it can easily be metabolized like 1,25-D3. ATRA can also be metabolized by CYPs; CYP2C8, CYP3A4, CYP2C9, CYP26A1 and CYP6B1 (Tornio et al. 2008; Nadin and Murray 1999). For this reason, during the treatments by using the administration of ATRA, I3C supplementation or I3C rich food consumption, may be contraindicated since I3C may induce and increase the overexpression of CYPs which metabolize ATRA!. On the other hand, not all prodrugs are effected adversely by I3C. Aminoflavone (AF; +H-1-benzopyran-4-one, 5-amino-2-(4-amino-3-fluorophenyl)-6,8-difluoro-7-methyl, NSC 686288), a synthetic flavonoid compound whose natural form is exist in fruits and vegetables is being used in cancer treatments with its apoptotic effect (Akama et al. 1996; McLean et al. 2008; Callero et al. 2012). Aminoflavone's anticancer effect is claimed as different from the prodrugs, the CYP inhibitors, mentioned above, since it seems closely related to Sulfotransferase (SULT) activity. The inhibition of SULTs and CYP enzymes by natural flavonoids blocks the antiproliferative

activity of Aminoflavone (meng et al. 2006) and this antiproliferative activity of Aminoflavone (Meng et al. 2006) and this clearly indicates that the anticancer effect of Aminoflavone is not related with CYPs, but even enhanced by CYPs (Pobst and Ames 2006). Confirmingly, Aminoflavone produces S-phase arrest in the SULT1A1-transfected and CYP-induced but not in the MCF-7 human breast cancer cells which SULT1A1 is not transfected and CYP is not induced (meng et al. 2006), all of which indicate that sulfotransferase and CYPs sensitize the cancer cells to aminoflavone. The anticancerogenic effects of other prodrugs are activated by CYP, like aminoflavone, are DMU-135 and phortress. DMU-135 is metabolized within tumours only by CYP1B1 to its active metabolite, DMU-117, a tyrosine kinase inhibitor while phortress, a benzothiazole, shows its anticancer effect by targeting the aryl hydrocarbon receptor (AhR). Phortress is hydrolysed into a lyophilic compound, SF203, and SF203 is the main anticancerogenic compound which is metabolized under the activation of CYPs; 1A1 or 1B1 (Badal and Delgoda 2013) and kills cancer cells, leading to DNA damage. Similarly, resveratrol, the dietary polyphenol derived from grapes, berries, peanuts, plums and pines (Harikumar and Aggarwal 2008; Bishayee 2009), is metabolized into an anticancer agent, piceatannol, by CYP1B1 (Potter et al. 2002). When all the data and the anticancerogenic effect mechanisms belong to the prodrugs mentioned above; aminoflavone, DMU-135, Phortress and resveratrol, opposite to the treatments made by using the CYP inhibitors mentioned previously, as combined with I3C supplementation or I3C rich food consumption, may be suggested to be included during the treatments with these prodrugs, since I3C induces the activity of CYPs and increases the overexpression of them which may result in the activation of the mentioned prodrugs.



Foods rich in vitamin D, e.g. oily fish (like salmon, mackerel and sardines), cod liver oil, egg yolk, vitamin D fortified milk and dairy products, vitamin D fortified cereals and cereal products, vitamin D fortified orange juice and vitamin D fortified margarine (Holick 2006; Calvo et al. 2004) ~~Cruciferous~~

FIGURE 77

CURCUMIN and COUMARIN

Curcumin (diferuloyl methane), the naturally occurring yellow pigment derived from the rhizome of *Curcuma longa* (Lin et al. 2000), shows its anticancer effect in various mechanisms. In one of the mechanisms. Curcumin targets the effector caspases (the proteases; caspase-3-6 and 7) (Olsson and Zhivotovsky 2011). The methane induces apoptosis in various cancer cells by activating caspase-3, caspase-8 (Wu et al. 2010; Anto et al. 2002; Su et al. 2006; Sikora et al. 2006).

Caspase activation begins with the binding of Fas ligand to Fas which is a transmembrane receptor and inducer of apoptosis (O'Brien et al. 2005). The binding of Fas ligand activates caspase-8 and then activates caspase-3 through direct proteolytic processing. Caspase-8 cleaves BID which is a protein, situated in extrinsic apoptotic signaling between death receptors and mitochondria. The protein, BID, also acts as an inductor of permeabilization of the outer mitochondrial membrane (Kantari and Walczak 2011; Barnhart et al. 2003). The cleaved BID promotes the release of cytochrome c, an electron carrier molecule between the two mitochondrial membranes. The cleavage of BID also forms the large quaternary protein, apoptosome. Finally, apoptosom formation activates caspase-9 which activates other caspases, -3,-7 and -2. The activated caspases proteolyze DNA leading to the programmed cell death, apoptosis (Cullen and Martin 2009). The anticancer drugs which induce caspase activity, namely; costunolide, mitomycin c, cisplatin, garcinol, brefeldin A, valinomycin, piceatannol, kinetin riboside, lipase inhibitor, THL (tetrahydrolipstatin), imiquimod, SC560, romidepsin, ouabain, digoxin, proscillaridin A, borrelidin, sanguinarine, bortezomib, MT-21, ionidamine (as combined with radiation), K858, saikosaponin A (a triterpene saponin derived from *Bupleurum falcatum L.*), CIL-102 and prodigiosin, may show better anticancerogenic effect if they are administered as combined with coumarin (the benzopyrone chemical) and coumarin rich foods like cinnamon, cinnamon containing foods (Bollin and Sorensen 2014) and *Curcuma longa* (Lin et al. 2000), since coumarin, like curcumin, induces apoptosis via the caspase activation (Wu et al. 2010; Anto et al. 2002; Su et

al. 2006 and Sikora et al. 2006), like the mentioned drugs. This synergism may result in a much greater caspase activation, leading to a stronger anticancer potential of these drugs.

Also, the anticancer drugs (which are cited in sulforaphane part with their references as related to their caspase inducing effects); sunitinib, sorafenib, reolysin, toyocamycin, sangivamycin, tetrandrine, bortezomib, paclitaxel, brefeldin A, sanguinarine, radicicol, porthenolide, geldanamycin, the gene therapies; Apaf1, FADD, Smac/DIABLO, retraspmcin, SNX-2112, daunorubicin, doxorubicin, etoposide, mitomycin c, cisplatin, dactinomycin, honokiol and MG-132, may show greater anticancer effect by activating caspases more, if they are administered as combined with sulforaphane rich foods (e.g. white cabbage, broccoli, red cabbage, caukliflower, Brussels sprouts, radish, mustard, turnip and Chinese kale), since sulforapahen rich foods (which are referred as caspase inducers with their references in the related part) and coumarin rich foods show their anticancer effects by activating caspase enymes, like all the mentioned drugs.

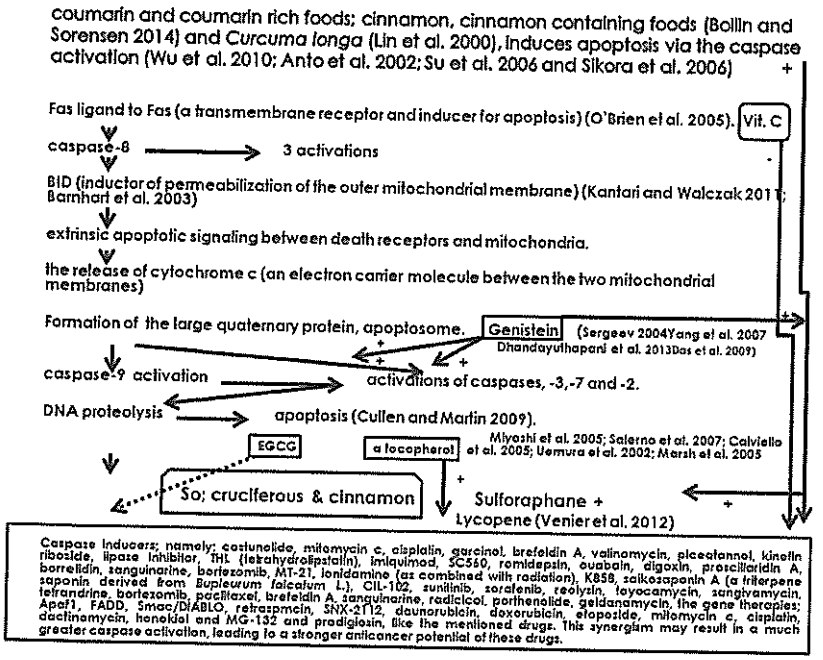


FIGURE 78

The cyclo-oxygenase (COX) enzymes whose overexpression via the certain stimuli as mitogens, cytokines and growth factors acts as inflammatory as carcinogen (Mazhar et al. 2005; Fernandez et al. 2003; Koehne and Duboid 2004; Sandler and Dubinett 2004; Hill et al. 2012; Lazar et al. 2008). On the other hand, curcumin has been claimed to inhibit the overexpression of COX enzymes in human colon (Goel et al. 2001), non-small cell lung (NSCLC) (Lev-Ari et al. 2014), skin (Chun et al. 2003), pancrease (Swamy et al. 2008), oral (Sharma et al. 2006) and prostate cancer cells (Fernandez-Martinez et al. 2009), improving the prognosis in all the mentioned cancer types. Therefore, the combination of curcumin and curcumin rich foods; cinnamon, cinnamon containing foods and *Curcuma longa*, as combined with the administration of the anticancer drugs which inhibit COX activity; sunitinib, celecoxib, magnolol, honokiol, eugenol, bis-eugenol, tetrandrine, 17AAG, raloxifene, rofecoxib, nafroxen, dexamethasone, hydrocortisone, triamcinolone acetonide, methyl prednisolone and beclomethasone diproprionate (the drugs that were cited in 'Sulforaphane' part with their references who found the related effects of each drug on COX activity), may improve the anticancer effects of these drugs more because of their synergism via the inhibition of COX activity. On the other hand, sulforaphane inhibits COX activity like curcumin and the mentioned drugs and thus, sulforaphane rich foods; white cabbage, broccoli, red cabbage, cauliflower, Brussels sprouts, radish, mustard, turnip and Chinese kale, may enhance the synergism among curcumin, sulforaphane and these drugs and finally, the anticancer effects of them.

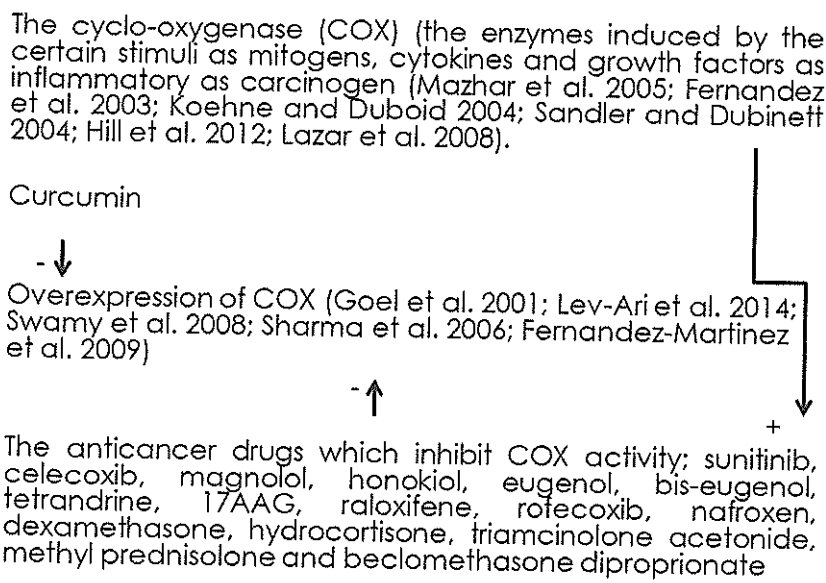


FIGURE 79

Coumarin's other anticancer effect is formed by activating the antioxidant enzymes; glutathione S-transferase and Nrf2 (Prince et al. 2009). Thus, if the vitamin A rich foods; collards, cabbage, Brussel sprouts, broccoli, apple, banana, peer, avocado, grape leave, lettuce, mango, melon, okra, onion, orange, green pepper, spinach, strawberries, cauliflower, potato, leek, parsley, cucumber, cod fish, cottage cheese, coconut and the anticancer drugs; 6-DG, oltipraz, zerumbone, are combined with coumarin and coumarin rich foods, their anticancer effects may increase, since coumarin and sulforaphane activate GST and Nrf2 (phase II enzymes). Coumarin also activates p38, the apoptotic protein which decreases the expression of cyclin D, a protein to regulate cell cycle progression (Zhon et al. 2014). Thus, the combination of coumarin and coumarin rich foods and the administration of the anticancer drugs which activate p38 (and whose p38 activating effects with their related references referred in sulforaphane part); cisplatin, transplatin, platinum (IV) chloride, brefeldin A, thapsigargin, tunicamycin, tamoxifen, betulinic acid, honokiol, bortezomib, 4-phenyl-3-betulinic acid (PBA), vorinostat, geldanamycin, raloxifen, paclitaxel

and panaxydol, may yield a much stronger anticancer effect, since both coumarin and coumarin rich foods and the mentioned drugs activate p38 and as a result, decrease the expression of cyclin D, inhibiting cell cycle progression.

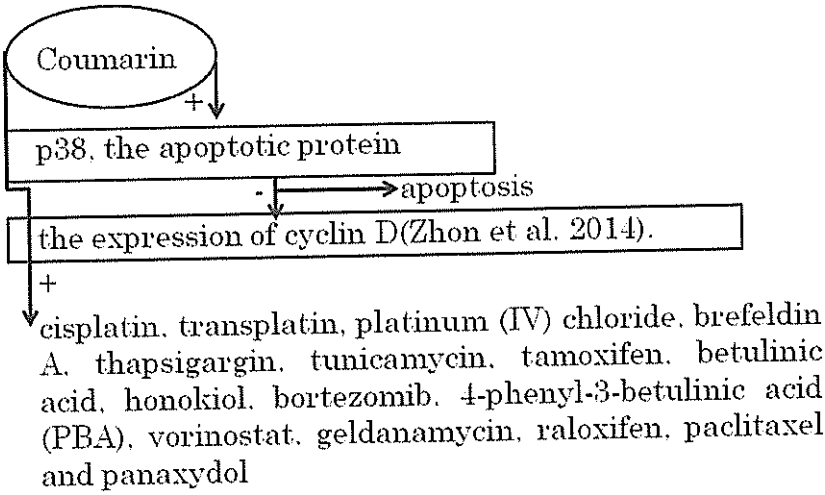


FIGURE 80

Hem oxygenase-1 (HO-1) produce teratogens; carbon monoxide, biliverdin and free iron which can be inhibited by coumarin and coumarin rich foods (Ballin and Sorensen 2014; Kim et al. 2014, Booth et al. 2006). Therefore, the treatments which target (HO-1) inhibition; tin (IV) protoporphyrin 1 dichloride (SnPP), zinc (II) protoporphrin IX (ZnPP), zinc (II) deuteroporphyrin IX-2, 4 bisethyleneglycol, imidazole-based compounds (8, 9,10R,10S,11,12,13,3), caveolin-1, calcineurin, siRNA, crom mesoporphyrin (CrMP), metformin, tin-mesoporphyrin, OB-24 ([2-(4-bromophenyl)ethyl]-2-[1H-imidazol-1-yl)methyl]-1,3-dioxolone hydrochloride), zinc mesoporphyrin (ZnMP), PEG-ZnPP (pegylated zinc protoporphyrin), the drugs whose references as related to their inhibition on (HO-1) have previously been cited, may have a much stronger anticancer effect, if they are administered as combined with coumarin and coumarin rich foods while enterolactone (flaxseed, sunflower, sesame, pumpkin seeds), capsaicin, dihydrocapsaicin (hot

pepper and hot pepper containing foods), matairesinol (whole grains), lariciresinol (sesame and Brassica vegetables, esculetin, coumarin (red clover, cinnamon) and coumarin containing foods and finally, sulforaphane and sulforaphane rich foods; white cabbage, broccoli, red cabbage, cauliflower, Brussels sprouts, radish, mustard, turnip and Chinese kale, should better be avoided during the mentioned treatments since these food substances induce HO-1 and subsequently may increase the teratogen production rate as previously mentioned with their related references.

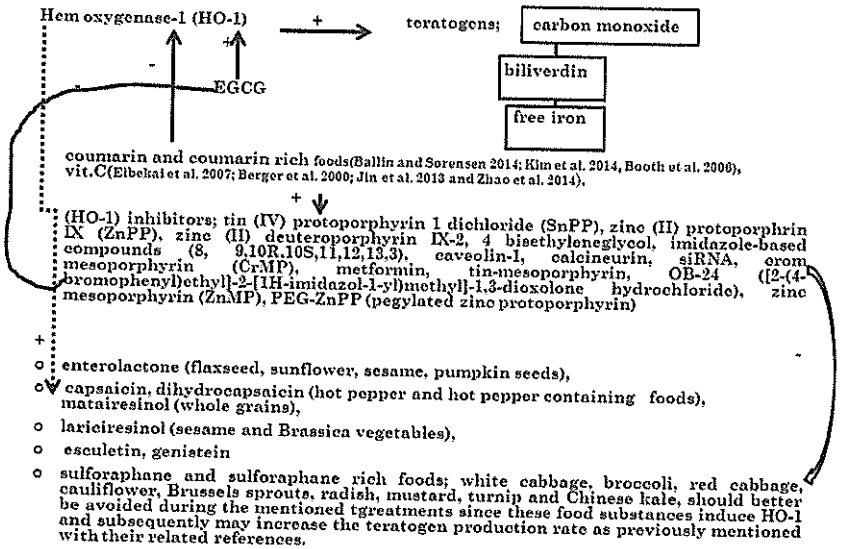


FIGURE 81

The effect of coumarin on cancer via the P450/CYP1A1 is still unclear and unknown. Urgent studies in near future to highlight the possibility of a possible anticancer effect of the bioflavonoid are required.

Coumarin may yield anticancer effect by gradually decreasing the expression of proteins which are vital in GO and G1 (resting and growth phases of cell proliferation), which may have led to the GO/G1 arrest while the same bioflavonoid also inhibits the expression of the antiapoptotic proteins; Bcl-2 and Bcl-xL and increases the anti-apoptotic protein, Bax (Chuang et al. 2007).

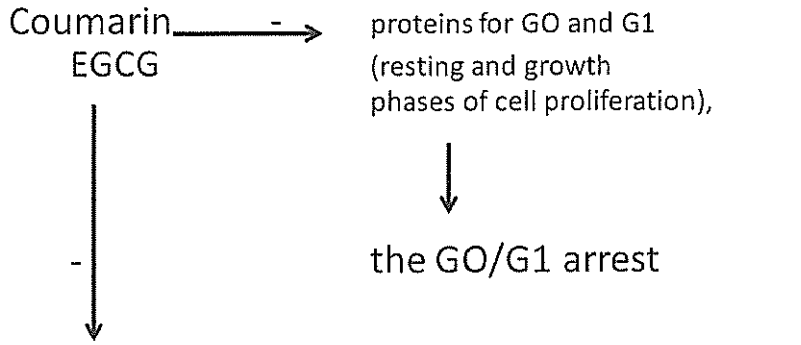


FIGURE 82

Coumarin induces the depolarization of mitochondrial membrane which triggers ROS production (Chuang et al. 2007, Rasul et al. 2011, Du et al. 2006 and Lupini et al. 2013). Therefore, its combination with the anticancer drugs (which are previously cited with their references as related to their ROS inducing effects); sunitinib, sorafenib, tetrandine, cisplatin, bortezomid, vorinostat, MG-132, metformin, thapsigargin, tunicamycin, 17AAG, DBeQ, ritonavir and brefeldin A, may increase the anticancer effect of these drugs since this synergism may increase the amount of ROS to target tumor. The addition of resveratrol and resveratrol rich foods (e.g., peanuts, grapes and blueberries) and sulforaphane and sulforaphane rich foods (e.g., white cabbage, broccoli, red cabbage, cauliflower, Brussels sprouts, radish,mustard, turnip and Chinese kale) into the anticancer diet besides coumarin and coumarin rich foods during the treatments with these drugs, may increase the anticancer potential of the drugs since resveratrol and sulforaphane, like coumarin and the drugs, increase ROS production to kill cancer cells (as previously mentioned in related parts with their references) which target cancer cells. Coumarin has also been claimed to be in antagonistic activity for ERIpha the estrogen receptor, which has long been associated with the progress of breast cancer (Xu et al. 2014, Panno

et al. 2012, Chen et al. 2004). Thus, tamoxifen, raloxifen, fulvestrant, C1618, nafoxidine, hexestrol, dienestrol treatments should be combined with resveratrol and resveratrol rich foods (e.g. peanuts, grapes and blueberries) (whose references as related to the inhibitory effect of the bioflavonoid on ERalpha are previously cited) and sulforaphane and sulforaphane rich foods as ER alpha antagonists (Ramirez and Singletary 2009) (rich in e.g. white cabbage, broccoli, Brussel sprouts, radish, cauliflower, mustard, turnip, Chinese kale, red cabbage), since all the mentioned drugs and bioflavonoids may inhibit ERalpha more, as in their combination, as compared with their sole administrations.

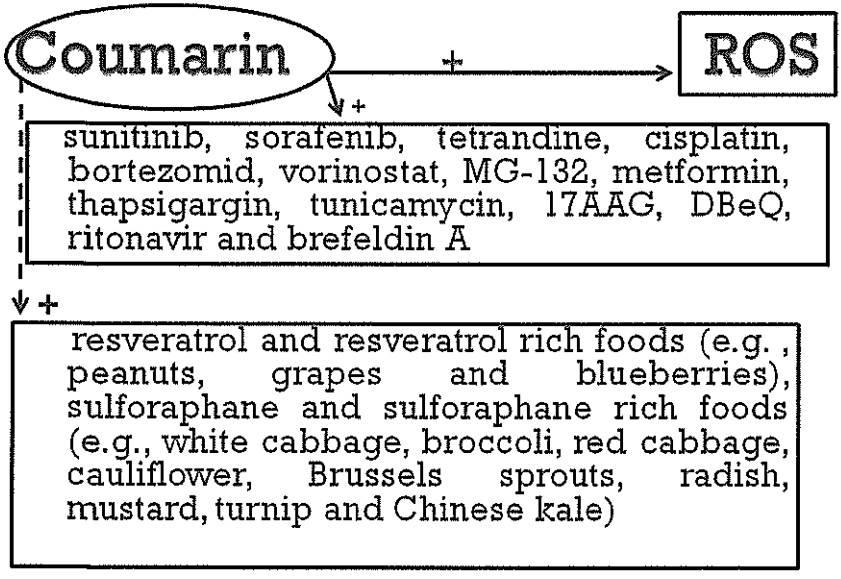


FIGURE 83

The overexpression and overactivation of Hedgehog (Hh) signaling which begins with the binding of Hedgehog (Hh) protein to patched 1 (Ptch 1, a protein receptor) and inhibits another transmembrane protein, smoothenes (Smo), activating it as an oncogene. Thus, the Hedgehog signaling appears as one of the anticancer strategies as previously mentioned. Curcumin and curcumin rich foods inhibit Hedgehog signaling (Elamin et al. 2010; Lian et al. 2015; Huang et

al. 2013) which may explain another anticancer effect mechanism of curcumin. Besides, resveratrol and resveratrol rich foods like grapes, blueberries, raspberries, mulberries, geinstein and genistein rich foods like; currants, raisins, satsumas, Brazil nut, chestnut, coconut, hazelnut and sesame seeds, Epigallocatechin gallate (EGCG) rich foods; white tea, green tea, black tea, dark chocolate, fava beans, pears, raspberries, cherries, blackberries and apples and finally curcumin and curcumin rich foods; turmeric, cinnamon, cinnamon containing foods; *Curcuma longa* and ginger (the food substances all of whose references as related to their effects on the Hedgehog signaling, including their food sources, are cired in 'resveratrol' part) should be included as combined during the administrations of the anticancer drugs which target Hedgbehog signaling namely; SANT1-SANT4, CUR-61414, HhAntag-691, GDC-0449, saridegib, phthaladines, mukul, guggulsterone, itraconazole, NVP-LDE225, TAK-441, XL-139, HTS piperidines, MRT-92, MRT-83, PF-04449913, N-acylethanolamides, endocannabionids, IPI926, BMS-833923, LEQ506, GANT61, ribotnikinin, HPI1-4, 2-acylglycerols and 2-alkylglycerol, since these drugs (whose effects on the signaling with their references are cited in the same part, Resveratrol), may be in a strong synergism to inhibit Hedgehog signaling more, in case of the involvement of the mentioned foods into the anticancer diet.

p-Akt (serine/threonine-specific protein kinase) which plays a key role in multiple cellular processes like glucose metabolism and cell proliferation may be a carcinogenic factor if overexpressed as previously indicated. Curcumin is claimed to inhibit p-Akt (Yu et al. 2008; Johnson et al. 2010; Kondo et al. 2013). Therefore, the anticancer drugs which target pAkt namely; LY29002, SF-1126, NVP-BEZ235, XL147, XL765, ISC-4, GSK690693, MK-2206 (which has strong synergistic effects with the other anticancer agents;erotinib, lapatinib, doxorubincin, camptothecin, gemcitabine, 5-FU, carbolatin and docetaxel), fused pyrimidines, phosphatidylinositol (3-5) triphosphate (PIP3), GDC-0041, celecoxib, 7-hydroxystarosporine(UCN-01), BX-795 BX-912 and BX-320, CCT12830, GDC-0068, perifosine (Gills and Dennis 2009), GSK-2141795, GSK2110183 (Dumble et al. 2014), Ipatasertib (GDC-0068), Afuresertib (GSK2110183), AT13148, PF-0461502, AT867 and triciribine administrations may yield greater anticancer potential if combined with

an anticancer diet that targets p-Akt; resveratrol and resveratrol rich foods (grapes, blueberries, raspberries, mulberries), epigallocatechin-3-gallate (white tea, green tea, black tea, dark chocolate, fava beans, pears, raspberries, cherries, blackberries and apples) and curcumin (*Curcuma longa*, ginger and cinnamon), since all these nutrients may increase the inhibitory potential of the mentioned drugs on p-Akt (the references as related to the inhibitory effects of the nutrients and the drugs are previously cited in 'resveratrol' part).

Curcumin may be in anticancer effect due to its up-regulating effect on the tumor protein, p53, which prevents cancer formation and thus acts as tumor suppressor as previously indicated (Liontas and Yeger 2004; Ye et al. 2015; Watson et al. 2010; Song et al. 2005).

The anticancer effects of the treatments by p53 activators; benzodiazepinedione (BDA) which interacts with the p53-binding pocket of Mdm2 and MI-219, MI-63 and MI-43, the spiro-oxindole compounds which mimic Mdm2E3, Mdm2-containing residues, CDB3 (a short synthetic nine-residue peptide, derived from p53-binding protein 2, a known p53-binding protein that interacts with the p53 core domain and upregulates it, p53 C-terminal peptide (peptide 46, which is derived from p53 C-terminal region) which increases sensitivity in radio-cancer therapy, especially in (wild-type) p53 cancer cells, CP-31398 (the small molecule with the activity to change p53 conformation from mutant to wild type and stabilizes the core domain and enhance transcriptional activity of p53 while upregulating the p53 target genes; p21WAF1/Cip1 and KILLER/DR5, 37AA, the peptide which consists of 37 amino acids from p53 and induces apoptosis through activation of p53/p73 target genes), JJ78: 12 (another small bioactive molecule which depolymerizes tubulin proteins and activates p53), tenovin-6 (the water soluble analog of tenovin-1) which induces apoptosis while activating p53 and inhibiting SIRT1 and SIRT2 and tenovin-1 (which are cited with their related reference citations as related to their activating effects on p53), may show much stronger effect if curcumin and curcumin containing foods and plants (*Curcuma longa*, ginger and cinnamon) and resveratrol and resveratrol rich foods (whose p53 activating effects are cited in the part of 'resveratrol'), like grape, blueberries, raspberries and mulberries) forms the dominant part of the anticancer diet during

the treatments due to the synergism of the drugs and bioflavonoids, all of which induce the upregulation and activity of p53.

NAT (N-acetyltransferase), the enzyme which catalyzes the detoxification of cancerogenic arylamines, as previously mentioned in I3C part, during the detoxification by NAT-1 and NAT-2, may biotransfer these carcinogen substances though it is the detoxifier of the carcinogens. Therefore, their overexpression like in many cases of cancer, may worsen the prognosis (Lang et al. 1986). Curcumin inhibits NAT activity (Chen et al. 2003). On the other hand, I3C and I3C rich foods (e.g. cruciferous vegetables) prevent the polymorphism of NAT2 which results in the formation of arylamine carcinogens. The inhibition of NAT activity and the prevention of NAT from polymorphism by the means of curcumin and I3C rich foods during the treatments by NAT inhibitors; the rhodanine analog ((Z)-5-(2'-hydroxybenzylidene)-2-thioxothiazolidin-4-one (Rhod-o-hp) with a minimal toxicity opposite to rhodanine) (Russell et al. 2009), tamoxifen (Lu et al. 1002; Lee et al. 2004),cisplatin (Ragunathan et al. 2008), disulfiram (Malka et al. 2009), acetaminophen (Rothen et al. 1998), paclitaxel (Hsia et al. 2004), may result in a stronger anticancer effect of the mentioned drugs via the inhibition of NAT and prevention of NAT from its polymorphism.

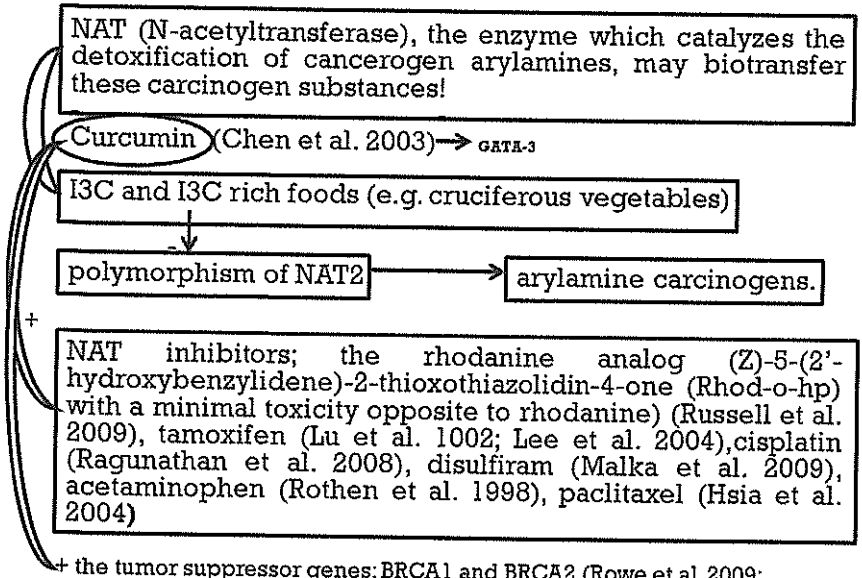


FIGURE 84

The inhibition of GATA-3 (trans-acting T-cell-specific transcription factor), a protein which regulates luminal epithelial cell differentiation in the mammary gland, is another key mechanism for the anticancer effect of curcumin (Chong et al. 2014). Glucocorticoids (Liberman et al. 2009) and fluticasone (a corticosteroid) (Maneechotesuwan et al. 2009) treatments may benefit from the involvement of curcumin and curcumin rich foods into the anticancer diet via the inhibition of GATA-3. Note that, I3C (as previously mentioned in the related part), also inhibits GATA-3 and thus, I3C rich food additions into the anticancer diet may even increase the anticancer potential of the glucocorticoid and corticosteroid treatments more.

Curcumin involvement into the anticancer diet may be beneficial due to its inducing effect on BRCA1 and BRCA2 genes but unfortunately, there is no any study as related to the effects of any anticancer drug on these tumor suppressor genes. Such studies is urgently needed to highlight the anticancer drugs which induce BRCA1 and A2 and

subsequently, the possible synergism of these drugs with curcumin and I3C, BRCA1 and A2 inducing bioflavonoids.

Finally, curcumin inhibits GRP78 (Chang et al. 2015), a central regulator of endoplasmic reticulum (ER) function because of its protein folding capacity as a chaperon. The anticancer drugs which inhibit the chaperon's activity; sunitinib, sorafenib, tetrandine, cisplatin, bortezomid, vorinostat, MG-132, metformin, thapsigargin, tunicamycin, versipelostatin, tanespimycin, HKH40A, WMC79, pyrivinium pamoate, eeyarestatin, metformin and bortezomib combination, 17AAG, DBeQ, ritonavir and brefeldin A, may benefit from coumarin since coumarin inhibits GRP78 activvity as similar to these drugs. But I3C and I3C rich foods (e.g. cruciferous vegetables; broccoli, cabbage, cauliflower, bok choy and Brussels sprouts) and resveratrol and resveratrol rich foods (e.g. peanuts, grapes and blueberries) induce the chaperon activity (Galluzzi et al. 2012; Park et al. 2007) and thus, may be contraindicated with these drugs while (-)-epigallocatechin gallate (EGCG), like curcumin in the diet may improve the anticancer potential of the mentioned drugs via the inhibition of the chaperon.

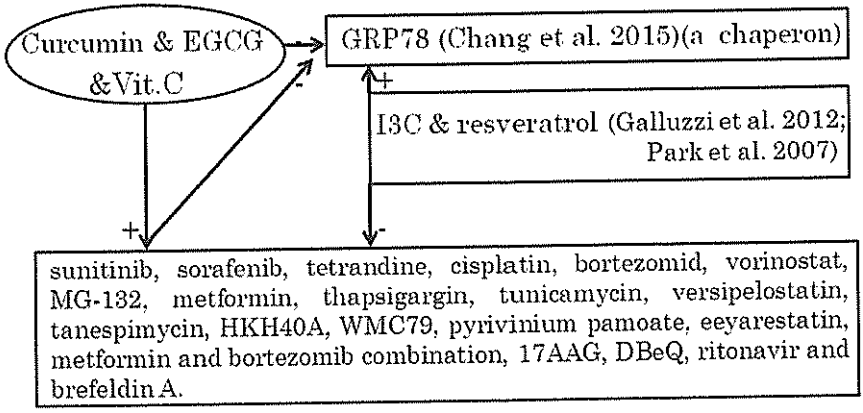


FIGURE 85

Coumarin induces the depolarization of mitochondrial membrane which triggers ROS production (Chuang et al. 2007, Rasul et al. 2011, Du et al. 2006, and Lupini et al. 2013). Therefore, its combination with

the anticancer drugs (which are previously cited with their references as related to their ROS inducing effects); sunitinib, sorafenib, tetrandrine, cisplatin, bortezomib, vorinostat, MG-132, metformin, thapsigargin, tunicamycin, 17AAG, DBeQ, ritonavir and brefeldin A, may increase the anticancer effect of these drugs since the synergism between these drugs and coumarin and coumarin rich foods, may increase the amount of ROS to target tumor.

The addition of resveratrol and resveratrol rich foods (e.g. peanuts, grapes and blueberries) and sulforaphane and sulforaphane rich foods (e.g. white cabbage, broccoli, red cabbage, cauliflower, Brussels sprouts, radish, mustard, turnip and Chinese kale) into the anticancer diet besides coumarin and coumarin rich foods during the treatments with these drugs, may increase the anticancer potential of the drugs since resveratrol and sulforaphane, like coumarin and the mentioned drugs, increase ROS production to kill cancer cells (as previously mentioned in the related parts with their references).

Coumarin has also been claimed to be in antagonism for ERalpha, the estrogen receptor, which has long been associated with the progress of breast cancer (Xu et al. 2014; Panno et al. 2012; Chen et al. 2004). Thus, tamoxifene, hexestrol, raloxifene, fulvestrant, C1618, nafoxidine, hexestrol, dienestrol treatments should be combined with resveratrol and resveratrol rich foods (e.g. peanuts, grapes and blueberries) (whose references as related to the inhibitory effect of the bioflavonoid on ERalpha are previously cited) and sulforaphane and sulforaphane rich foods as ERalpha antagonists (Ramirez and Singletary 2009) (rich in e.g. white cabbage, broccoli, Brussels sprouts, radish, cauliflower, mustard, turnip, Chinese kale, red cabbage), since all the mentioned drugs and bioflavonoids may inhibit ERalpha more, when they are in the same combination, as compared with their sole administration.

KAEMPFEROL

The polyphenol antioxidant, which has the beneficial effects in reducing the risk of chronic disease especially cancer, kaempferol, is a modulator of a number of key elements in cellular signal transduction pathways linked to apoptosis, angiogenesis, inflammation and metastasis (Chen and Chen 2013). The polyphenol is abundantly found in tea, broccoli, apple, strawberries, beans (Somerset and Johannot 2008), kale, endive, leek, tomato, grapes, blueberries, cherry,, parsley, plum, apricot, onion, herbs; *Ginkgo biloba*, *Tilia* spp., *Equisetum* spp., *Moringa oleifera*, *Sophora japonica* and propolis (Calderon-Montano 2011; Manach et al. 2004). There exist many pathways for translating chemical messages into physical changes in gene expression, one of which is the MAPK/ERK pathway. The pathway is a chain of proteins in the cell that communicates a signal from a receptor on the surface of the cell in the DNA in the nucleus of the cell. The signal starts when a signaling molecule binds to the receptor on the cell and ends when the DNA in the nucleus expresses a protein and produces change in cell and cellular phases like cell division. The proteins in the pathway are MAPK (mitogen-activated protein kişnases), ERK (extracellular signal-regulated kinases). So, the MAPK pathway plays an integral role in both the promotion and regulation of cell growth. For example, the proteins; ERK 1 and 2 activate the 90-kDA ribosomal S6 kinases which are sensitive to growth factors (Frodin and Gammeltoft 1999).

NF-kB (Nuclear Factor kappa-light-chain-enhancer of activated B cells), a protein complex that controls the transcription of DNA, cytokine production and cell survival, is activated by IL-1beta, the protein which activates inflammation that promotes invasiveness (Apte et al. 2006). Kaempferol inhibits IL-1beta which results in the blockage of NF-kB (Lee et al. 2014). NF-kB, the activator of ERK1/2 (Dhawan and Richmond 2002) cannot activate anymore because of its inhibition by Kaempferol. Not only by blocking NF-kB via the inhibition of IL-1beta, but also being able to reduce the protein phosphorylation of ERK, the flavonoid attenuates the MAPK/ERK signaling, contributing to the

inhibition of cancer (Chen et al. 2013). For this reason, the anti-cancer potential of anti-cancer drugs which kill cancer cells by inhibiting MAPK/ERK signaling and ERK proteins, namely; vorinostat, ritonavir, radicicol, tamoxifen, geldanamycin, lapatinib, fulvestrant, PD98059, UO126, hoinokiol, SNX212 may increase if they are administered during a cancer diet rich in kaempferol, the diet which includes tea, broccoli, apple, strawberries, onion, capsicum pepper, cherry, celery, parsley, plum, apricot, the herbs; Gingko bloba, Tilia spp., Equisetum spp., Moringa oleifera, Sophora japonica and propolis. But it may be vitally important that the limitation of sulforaphane during the diet and the limitation of sulforaphane rich foods; white cabbage, Brussel sprouts, radish, mustard, cauliflower, turnip and Chinese kale may be helpful to help to improve the apoptotic effect of the mentioned anti-cancer drugs since sulforaphane induces MAPK/ERK signaling (Jo et al. 2914).

Vascular Endothelial Growth Factor (VEGF), a signal protein which is produced by cells to stimulate vasculogenesis (the process of blood vessel formation) and angiogenesis (the process of blood vessel formation) and angiogenesis, and hence it may be an initiator of cancer. The protein has also an ability to regulate the trafficking of growth factor receptors and integrins, the trans membrane receptors that are bridges for cell to cell and cell to extracellular matrix interactions. These abilities of the protein may cause tumorigenesis in case of its overactivation or overexpression. VEGF-mediated signaling significantly contributes to hyperactivity of cancer stem cells and as a result tumor initiation (Goel and Mercurio 2013). The cancerogenic effect of the protein has also been confirmed by Liang et al. (2006; Skobe et al. (2001); Oommen et al. (2011); Rini and Small (2005) and Jacobsen et al. (2004). On the other hand, kaempferol has strong inhibitory effects on VEGF and also HIF-1alpha (hypoxia-inducible factor 1-alpha) (Luo et al. 2008) through the PI3-kinase/Akt signaling with a significant decrease in p-Akt.

The PI3-kinase/Akt signaling pathway is involved in protein synthesis, prolşiferation and survival. PI3-kinase (phosphatidylinositol-4,5-bisphosphate 3–kinase) promotes PIP3 (phosphatidylinositol 3,4,5 triphosphate) formation which translocates Akt, an enzyme which acts

as a key survival kinase in many cancers (Cheng et al. 2005; Manning and Cantley 2007).

The anti-cancer potential of the anti-cancer drugs which induce apoptosis by inhibiting VEGF; (Roskoski 2007; Chen et al. 2014) sorafenib (Wilhelm et al. 2008; Chang et al. 2012), bortezomib (Hammer et al. 2007); bortezomib and MPO250 (Fiedler et al. 2009), MG132 (Matsuo et al. 2010), MG262 (Meissner et al. 2009), KF58333 (a radicicol derivative) (Kurebayashi et al. 2010), 17-AAG, geldanamycin (Sanderson et al. 2006), SNX-2112 (Okawa et al. 2009; Friedman et al. 2013), honokiol (Wen et al. 2009; Bai et al. 2003), thapsigargin, bafilomycin A1 (Favia et al. 2014), budesonide, brefeldin A, monensin (Bandi and Kompella 2001), ritonavir (Vadlapatla et al. 2014; Pati et al. 2002), bevacuzimab (Ranieri et al. 2006), ranibizumab (Lowe et al. 2012), tamoxifen and vandetanib combination (Siegfried et al. 2012), tamoxifen, clomiphene, nafoxidine, ICI182,780 (Gagliardi et al. 1996), metformin (Dallaglio et al. 2014), paclitaxel (the drug is especially effective against radiation induced VEGF secretion, which should be taken into consideration in case of radiotherapy)(Toiyama et al. 2009), tunicamycin (Banerjee et al. 2008), tibolone (Sioulas et al. 2011) and PTK787/ZK222584(Wood 2000), may be improved if they are administered during the period of food consumption rich in kaempferol; tea, broccoli, apple, strawberries, beans, kale, endive, leek, tomato, grape, blueberries, capsicum pepper, cherry, celery, parsley, plum and apricot since the polyphenol, similar to the mentioned VEGF inhibitory drugs, inhibit VEGF and this may form a synergism, increasing the anti-cancer potentials of VEGF inhibitory drugs by kaempferol.

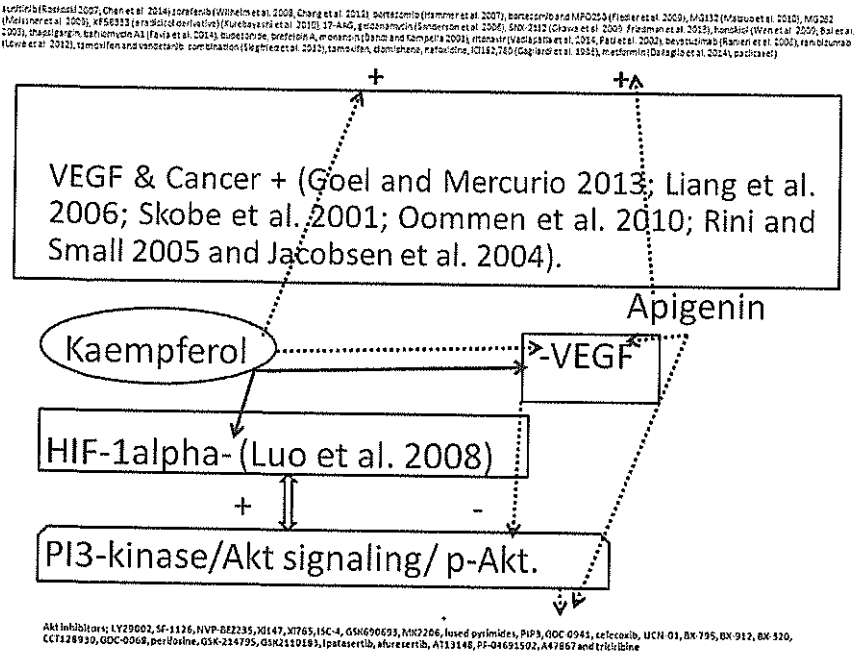


FIGURE 86

The flavanoid shows one of its anticancer effects via the inhibition on ERalpha which may be important, especially in the treatments of breast cancer (Hung 2004). The treatments using the anti-cancer drugs which inhibit ERalpha; nafoxidine, hexestrol, C1618 and dienestrol may result in more apoptosis if they are combined with a diet rich in kaempferol, since both the flavonoid and the mentioned anti-cancer drugs inhibit ERalpha and hence may form a synergy to kill breast cancer cells more.

Because of the inhibitory effect of the flavonoid on the activity of Akt, serine/threonine-specific protein kinae, the anti-cancer drugs; LY29002, SF-1126, NVP-BEZ235, XI147, XI765, ISC-4, GSK690693, MK2206, fused pyrimides, PIP3, GDC-0941, celecoxib, UCN-01, BX-795, BX-912, BX-320, CCT128930, GDC-0068, perifosine, GSK-214795, GSK2110183, Ipatasertib, afuresertib, AT13148, PF-04691502, A47867 and triciribine, which similarly inhibit the enzyme, may show stronger apoptotic effect if they are administered during a rich food consumption in kaempferol.

In spite of the studies which claim important anticancerogenic effects of the flavonoid, there is currently no study to highlight the association between the flavonoid and GRP78 (the central regulator and chaperon of endoplasmic reticulum), and also the flavonoid and Hedgehog signaling (which induce proliferation). The novel anti-cancer treatments which target GRP78 and hedgehog signaling may also involve kaempferol if its inhibitory effects on the chaperon and the signaling are determined by the studies in a very near future.

One important and also very special anticancerogenic effect of the flavonoid is claimed to be due the reducing effect of kaempferol on CDK1 levels. Cancer cells and normal cells pass through the cell cycles during proliferation and mitosis-promoting factor (MPF) is the key protein responsible for the transition from the G2 phase to the M phase, the phase in which the division forms. MPF serves a critical role in the pass from G2 to M phase and the protein is composed of a cyclin subunit and a kinase subunit which is termed 'cyclin-dependent kinase (CDK)'. Mitosis can only start with the CDK binding to the cyclin regulatory protein to activate MPF (Chen and Chen 2013). So, reducing the levels of CDK1 and MPF levels may be a novel target to induce apoptosis in cancer treatments. Confirming this, the flavonoid has been shown to reduce CDK1 levels in human breast cancer MDA-MB-453 cells (Choi and Ahn 2008). On the other hand, two of the most common anti-cancer drugs; sunitinib and sorafenib are claimed to increase CDK levels (Juengel et al. 2015). This risk may be alleviated if kaempferol rich foods are supplied during the treatments with the mentioned drugs.

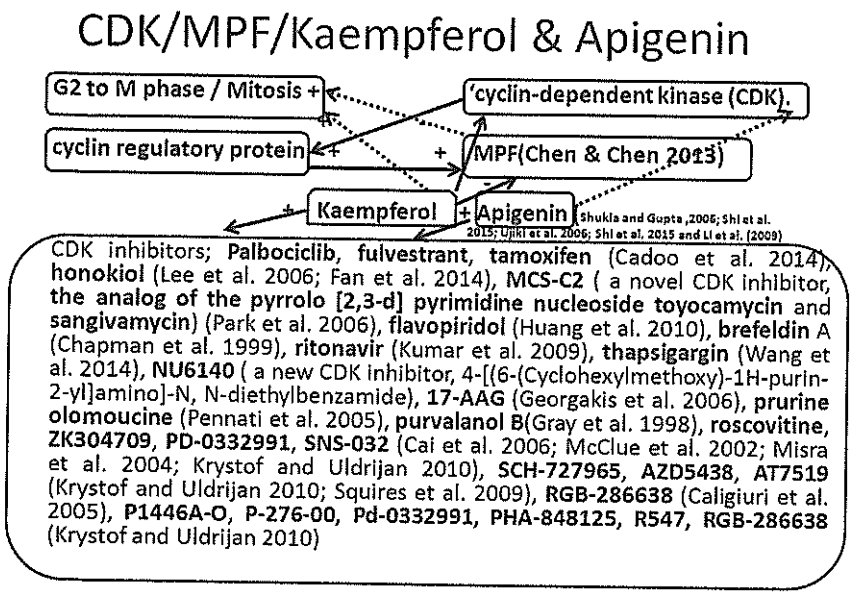


FIGURE 87

Palbociclib, fulvestrant, tamoxifen (Cadoo et al. 2014), honokiol (Lee et al. 2006; Fan et al. 2014), MCS-C2 (a novel CDK inhibitor, the analog of the pyrrolo [2,3-d] pyrimidine nucleoside toyocamycin and sangivamycin) (Park et al. 2006), flavopiridol (Huang et al. 2010), brefeldin A (Chapman et al. 1999), ritonavir (Kumar et al. 2009), thapsigargin (Wang et al. 2014), NU6140 (a new CDK inhibitor, 4-[(6-(Cyclohexylmethoxy)-1H-purin-2-yl]amino]-N, N-diethylbenzamide), 17-AAG (Georgakis et al. 2006), prurine olomoucine (Pennati et al. 2005), purvalanol B (Gray et al. 1998), roscovitine, ZK304709, PD-0332991, SNS-032 (Cai et al. 2006; McClue et al. 2002; Misra et al. 2004; Krystof and Uldrijan 2010), SCH-727965, AZD5438, AT7519 (Krystof and Uldrijan 2010; Squires et al. 2009), RGB-286638 (Caligiuri et al. 2005), P1446A-O, P-276-00, Pd-0332991, PHA-848125, R547, RGB-286638 (Krystof and Uldrijan 2010) may show stronger anticancer effect if they are administered during the food consumption rich in kaempferol, since both the flavonoid and the mentioned anticancer drugs reduce the level of CDKs. The synergism between them via the inhibition of CDKs may yield a greater level of apoptosis.

Nutrient starvation is one of the most direct method of promoting cell death (Chen and Chen 2013). On the other hand, kaempferol blocks cellular intake of glucose (Filomeni et al. 2010), interferes with oxidative phosphorylation through inhibiting ATP synthase (Li et al. 2012) and lowers mitochondrial membrane potential which destroys the proton gradient which is required by ATP synthase (Huang et al. 2010).

Kaempferol has also been found to inhibit the enzyme 'fatty acid synthase' (FAS) which is a key enzyme in the production of fat. Fat is necessary not only for energy production, but also for membrane structure. Thus, cancer cells like healthy ones, need the enzyme for membrane stability and energy production, even more than the healty cells (Brusselmans et al. 2005;. Menendez and Lupu 2007). Additionally, fatty acids are also the substrates for sphingolipid synthesis. Sphingolipids, such as ceramids and sphingosine-1-phosphate, are bioactive signaling molecules that generally suppress but sometimes promote tumors (Ogretmen and Hannun 2004). For this reason, the flavonoid may inhibit the signaling among cancer cells via the inhibition of sphingolipids as a result of the inhibition of FAS and fatty acid production which may be one of the reasons for the flavonoid's anticancer effect. Especially, that the anti-cancer drugs are selectively toxic to tumor cells (Pandey et al. 2012) and kaempferol is much less toxic to normal cells (Zhang et al. 2008), gain a crucial position to the flavonoid and the following FAS inhibitors; Orlistat (Keri et al. 2003), cerulenin (Royer and Townsend 1996; Kuhajda 2000), C75 (Kuhajda et al. 2007), C93 (Kuhajda et al. 2010; Orita et al. 2007), PARP inhibitors (a group of pharmacological inhibitors of the enzyme poly ADP ribose polymerase) (Ossovskaya et al. 2011), triazoles (Bahadoor et al. 2011), beta-lactones (Richardson et al. 2008), EGCG (Epigallocatechin-3-gallate) (Chung 1995), C247, GSK837149A (Flavin et al. 2011) and Omega 3 fatty acids (Lamaziere et al. 2013), as in combination as a nowel anticancer approach. Accordingly, it may be crucial to include the kaempferol rich foods; tea, broccoli, blueberries, cherry, strawberries, beans, leek, tomato, endive, kale, onion, grapes, parsley, plum, apricot, capsicum pepper, celery and also Omega 3 fatty fish since Omega 3, like kaempferol and the mentioned drugs, inhibit FAS, forming a synergy with kaempferol and the FAS inhibitors. On the other hand, out of all the flavonoids, kaempferol has

been found to reduce the expression of matrix metalloproteinase (Lin et al. 2013; Li et al. 2015; Choi et al. 2015).

Cancer cells disseminate to other tissues and induce metastasis by degrading their surrounding extracellular matrix (ECM), making a way to the vascular system. They use some special enzymes, namely 'metalloproteinases', to degrade ECM. High levels of metalloproteinases (MMPs) are associated with increased levels of tumor invasion (Deryugina and Quigley 2006). During cancer progress, thrombin and thrombin receptor-activating peptide induce MMP secretion which is paralleled by an increase the bridges for cell-cell and cell-extracellular matrix (ECM), which are crucial in cancer initiating signaling through cells (Radjabi et al. 2008). MMPs destroy ECM proteins such as fibrillin, collogen, fibronectin, cilia, surfactant proteins A and D immunoglobulins (Gaggar et al. 2011; Brennan et al. 2003; Tsuruga et al. 2007), all contributing to the dissemination of cancer cells in ECM. AG3340 (a hydroxamic acid derivative) (Garcia et al. 2002), BAY12-9566 (a butanoic acid analog) (Nozaki et al. 2003), CGS27023A (the latest entry into the metalloproteinase inhibitiors) (Kasaoka et al. 2008), marimastat (BB-2516, a hydroxamic acid analog) (Sinno et al. 2013), bryostatins (naturally occurring macrocyclic lactones), TIMPs (Tissue Inhibitors of Metalloproteinases) (Wojtowicz-Praga et al. 1997), lapatinib (Lin et al. 2014), BB-94 (Kirkegaard et al. 2014), tamoxifen (Wang et al. 2011), radicicol (Hsiao et al. 2013), UO126 (Horiuchi et al. 2004), metformin (Hwang and Jeong, 2010), celecoxib (Zhao et al. 2009), honokiol (Kim et al. 2010), 17AAG (Singh et al. 2015), raloxifene (Bellosta et al. 2007), tetrandrine (Zhou et al. 2013), naproxen (Kim et al. 2011), ibuprofen, rofecoxib (Wang et al. 2006), dexamethasone (Pross et al. 2002), bleomycin (Lagente et al. 2005), hydrocortisone (Aljada et al. 2001), methylprednisolone (Wong et al. 2000), MG132 (Meiners et al. 2004), vorinostat (Zhong et al. 2013), tunicamycin (Stricklin 1986), brefeldin A, arfaptin 1 (Ho et al. 2003), lactacystin (De Barros et al. 2007) and trichostatin A (Nasu et al. 2008), may show stronger apoptotic effect if they are administered during a keamepferol rich food consumption which includes; tomato, grape, apple, strawberries, tea, plum, apricot, blueberries, cherry, parsley, endive, leek, parsley, broccoli, kale, beans, capsicum pepper, herbs; Gingko biloba, Tilia

spp., Equisetum spp., Moringa oleifera, Sophora japonica and propolis since the foods and the anti-cancer drugs may form a synergy and hence may have got stronger anticancer effects via the inhibition of MMPs by kaempferol. It may be vitally important that the anticancer drugs, anandamide (Miyashita et al. 2012) and EMMPRIN CD147 (Sameshima et al. 2000) which have a side effect, the induction of MMPs, may be reduced if these drugs are administered as combined with kaempferol supplementation or the flavonoid rich food consumption, decreasing the rate of MMP induction by kaempferol.

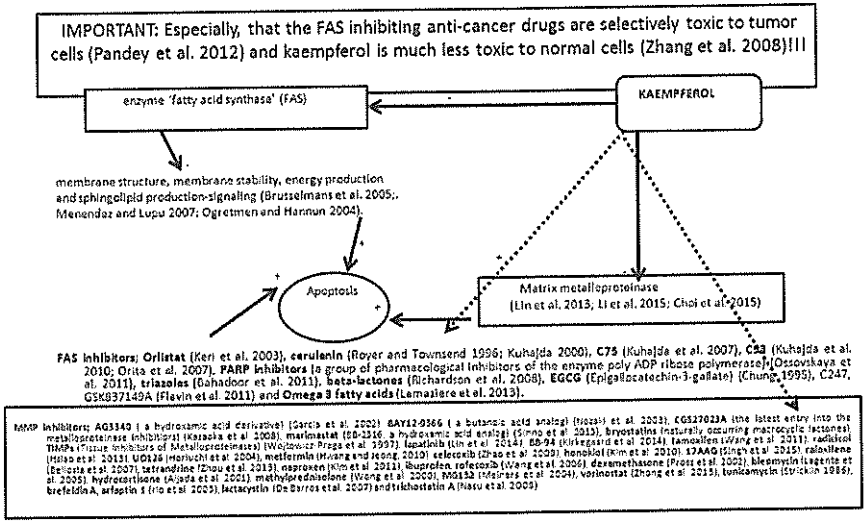


FIGURE 88

Kaempferol's other anticancerogenic effect is associated with its anti-inflammatory effect. The flavonoid inhibits COX-2, the enzyme which is responsible for the production of inflammatory hormones and the flavonoid also inhibits the cytokine, interleukin-1beta (IL-1β), which activates COX-2 (Lee et al. 2010, Yoon et al. 2013; Zhang et al. 2006). Therefore, the kaempferol rich foods; grapes, strawberries, apple, broccoli, tea, endive, blueberries, parsley, cherry, beans, kale, tomato, plum, apricot, capsicum pepper, the plants; *Gingko biloba*, *Talia* spp., *Equisetum* spp., *Moringa oleifera*, *Sophora japonica* and propolis, in addition to the B_6/folate rich foods; beef liver, tuna,

salmon, chicken breast, banana, ground beef, bulgur, squash, nuts, onion, spinach, turkey meat, tofu, raisins, watermelon, black-eyed peas, asparagus, peas, kidney beans, peanuts, crab, orange, yeast, egg, mustard green, green peas, Brussel sprouts, lettuce, avocado, asparagus cantaloupe, fish, milk and chicken breast, may enhance the anticancer potential of the following anticancer drugs which inhibit COX-2 and IL-1β; sunitinib, celecoxib, magnolol, honokiol, eugenol, bis-eugenol, tetrandrine, 17AAG, raloxifene, rofecoxib, nafroxen, dexamethasone, hydrocortisone, triamcinolone acetonide, methyl prednisolone and beclomethasone diproprionate, since all the mentioned anticancer drugs, kaempferol and B6/folate inhibit COX2 and IL-1β.

Tumor necrosis factor (TNF), a glucoprotein, was shown to induce the haemorrhagic necrosis of tumors as being dependent on conditions (Pennica et al. 1984). On the other hand, the pleiotropic cytokine, the cytokine which affects multiple systems while it is produced as a result of one of gene defects, can be a tumor-promoting cytokine. The latest review about the cytokine whether it is a tumor promoter or inhibiter suggests that blocking the TNF pathway in a variety of tumour models inhibits tumor growth (Lebrec et al. 2015). More important is that, the cytokine was found to mediate widespread systemic effects, mediating cachexia, anorexia, weight loss, anaemia, chronic infections, inflammation, and protein wasting that complicate cancer (Bradley 2008; Popa et al. 2007; Olmos and Llado 2014). The cytokine recruits adaptor molecules that create a signaling to activate Mitogen-activated Protein Kinase Kinase Kinases (MAP3Ks), known as MAPK (ERK), and transforming growth factor-β (TGFβ), an essential regulator of cell survival, whose deficiency induces markedly elevated apoptosis (Wang et al. 2012). The activation of both MAP3Ks and TAK1 by the cytokine leads to the activation of the inhibitor of kappa βalpha (Ikβα) which inactivates NF-kβ, the protein complex that controls transcription of DNA, cytokine production and cell survival due to the antiapoptotic factor FADD45β which is regulated by NFkβ. It should be importantly noted that, Tornatore et al. (2014) have found a D-tripeptide, DTP-3, to disrupt the GADD45β without any toxicity to normal cells. In spite of these tumor promoting effects of the protein, TNF was previously viewed as a cytokine which would kill tumor cells while sparing

normal cells. But then, it was realized that tumor cells did not have TNF receptors and were unresponsive to TNF. In fact, tumor killing was mediated by a Shwartzman-like neutrophil-mediated destruction and thrombosis of tumor blood vessels (Norman et al. 1996). TNF can signal cell proliferation and contribute to cell survival via the activation of NF-kB, but also AP-1 and Elk-1 (the oncogene proteins), phosphorylation of Etk (tyrosine kinase) which activates phosphatidylinositol 3-kinase (PI3K), VEGF and survival pathway (Pan et al. 2002; Zhang et al. 2003). On the other hand, the cytokine may induce apoptosis which is mostly based on its relation with the apoptotic enzymes, Caspases. TNF receptor-associated death domain protein (TRADD) and a serine/threonine kinase called receptor interacting protein kinase (RIPK)-1 form a signaling complex that recruits an adaptor protein known as Fas-associated death domain protein (FADD), forming a DISC (Micheau and Tschoop 2003). The DISC recruits and promotes autocatalytic activation of pro-caspases 8-10 which activate caspases 8, 10 and 6. The caspases start nuclear fragmentation, caspase-mediated cleavage of nuclear fragmentation, caspase-mediated cleavage of nuclear lamins and DNA fragmentation.

Since TNF has got dual effect on cancer as augmenting or apoptotic, the treatments have been administered either by inducing TNF or by blocking the cytokine. The isolated limb profusion of TNF in combination with the alkylatin agent melphalan (Grünhagen et al. 2006) and the selective TNF-induced expression of VEGF (Zhang et al. 1994) are some of the studies which targeted cancer cells by inducing the cytokine. On the other hand, the inhibition of TNF has been shown to inhibit cancer (Bertrand et al. 2015) by enhancing tumor infiltrating T lymphocytes and subsequently immune system while the activation of TNF-dependent NF-kB increases the resistance of tumor cells, especially breast and ovarian cancer cells, against the anticancer drugs, paclitaxel and docetaxel (Sprowl et al. 2012).

Currently, the inhibitors of TNF and NF-kB, namely; infliximab (Martius et al. 2015), etanercept (Roh et al. 2012), adalimumab (Neubauer et al. 2014), certolizumab, golimumab (Horiuchi et al. 2010), emetine, sunitinib malate, bithionol, narasin, tribromsalan, lestaurtinib (Miller et al. 2010), bortezomib (van der Heijden et al.

2009), 17-AAG (17-Allylamino-17-Demathoxygeldanamycin) (Wang et al. 2006), metformin (Kim et al. 2011), radicicol ((Youn et al. 2013), tunicamycin (Kim et al. 2013), geldanamycin (Malhotra et al. 2001), ritonavir (Wang et al. 2004), honokiol (Tse et al. 2005), vorinostat (Galimberti et al. 2009), celecoxib (Shishodia et al. 2004), tetrandrine (He et al. 2011), naproxen, indomethacin, sulindac, dexamethasone, curcumin, tamoxifen, resveratrol (Takada et al. 2004) seem to have gained more application than TNF inducers. These anti-cancer compounds may have greater anticancer effect during the treatments if they are administered with a diet rich in kaempferol, including; kale, apricot, apple, strawberries, blueberries, endive, parsley, grape, beans, broccoli, cherry, celery, capsicum pepper, onion, plum, leek, herbs; *Gingko biloba*, Tilia spp., *Moringa oleifera*, *Sophora japonica*, also resveratrol rich foods like; tea, orange, strawberries, lemon, peanut, grapes and blueberries and curcumin (in *Curcuma longa* and cinnamon, since all the mentioned flavonoids including kaempferol (Xiao et al. 2016) and the anti-cancer drugs may form a synergy via the inhibition of TNF/NF-kB, yielding a much stronger anticancer effect.

Caspase activity, which proteolyzes DNA and thus causes to the programmed cell death, apoptosis, is also induced by kaempferol (Lee et al. 2014; Halimah et al. 2015 and Luo et al. 2010). Therefore, costunolide (the stem bark of *Magnolia sieboldii*), cisplatin, mitomycin c, garcinol, brefeldin A, valinamycin, piceatannol, kinetin riboside, lipase inhibitor, THL, imiquimod, SC 560, romidepsin, ouabain, digoxin, proscillaridin A, borrelidin, sanguinarine, bortezomib, MT-21, lonidamine, K858, saikosaponin A, CIL-102 and prodigiosin, may show greater anticancer effect if they are administered during a kaempferol rich nutrition since the flavonoid and the mentioned anticancer compounds target cancer cells by activating caspases, forming a synergy. This synergy may be enhanced if the mentioned drug and diet combination also includes coumarin (e.g. *Curcuma longa* and cinnamon). On the other hand, Hem oxygenase-1 (HO-1) which produces teratogens, e. g. carbon monoxide, biliverdin and free iron, is induced by kaempferol (Hirose et al. 2009; Gao et al. 2010) and therefore kaempferol rich foods (e. g. broccoli, apple, kale, strawberries, plum, parsley, cherry, onion, tea, capsicum pepper, celery, endive, beans, herbs; *Gingko biloba*, *Tulia* spp., *Moringa*

oleifera and *Sophora japonica*, should better be avoided if they are consumed during the treatments by drugs which target HO-1; tin (IV) protoporphyrin 1 dichloride (SnPP), zinc (II) protoporphrin IX (ZnPP), zinc (II) deuteroporphyrin IX-2, 4 bisethyleneglycol, imidazole-based compounds (8, 9,10R,10S,11,12,13,3), caveolin-1, calcineurin, siRNA, metformin, tin-mesoporphyrin, zinc mesoporphyrin (ZnMP), PEG-ZnPP (pegylated zinc protoporphyrin) and OB-24. It should be noted that flax-seed, sunflower, sesame, pumpkin seeds, Brussel sprouds, broccoli, cinnamon, *Curcuma longa*, white cabbage, red cabbage, cauliflower, radish, mustard, turnip and chinase kale, briefly sulforaphane and coumarin rich foods, should similarly be avoided since they also induce HO-1 during the mentioned treatments which use the mentioned HO-1 inhibitors.

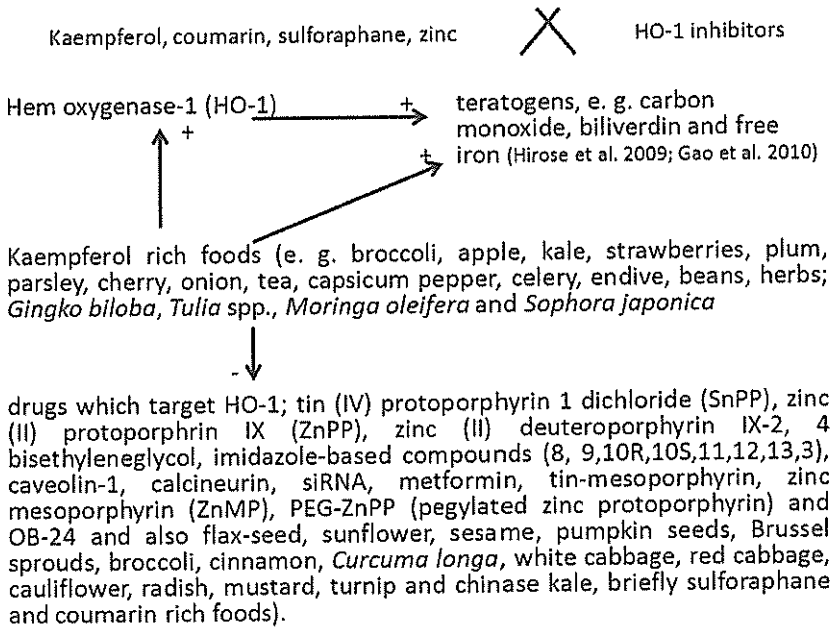


FIGURE 89

Kaempferol also shows its anticancer effect by inhibiting COX-2, the enzyme whose overexpression via to certain stimuli such as mitogens, cytokines and growth factors act as inflammatory and carcinogen (Lee

et al. 2010; Yoon et al. 2013; Liang et al. 1999). Therefore, the anticancer drugs; celecoxib, sunitinib, radicicol, sorafenib, metformin, magholol, hookiol, eugenol, bis-eugenol, tetrandrine, 17-AAG, raloxifene, rocecoxib, naproxen, dexamethasone, hydrocortisone, beclomethasone acetonide, methyl prednisolone, beclomethasone, hydrocortisone, triamcinolone acetonide, methyl prednisolone and beclomethasone diproprionate which similarly inhibit COX may have stronger anticancer potential if theyare administered during an anticancer diet rich in kaempferol (e.g.broccoli, apple, grape, endive, kale, leek, tomato, cherry, capsicum pepper, parsley, blueberries, celery, apricot, plum, strawberries, herbs; tea, *Ginkgo biloba*, *Sophora japonica*, *Moringa oleifera*, *Tulia* spp..) and curcumin (e.g. Curcuma longa and cinnamon) since all the mentioned anticancer drugs and both flavonoids inhibit COX and this synergy created may enhance the anticancer effect.

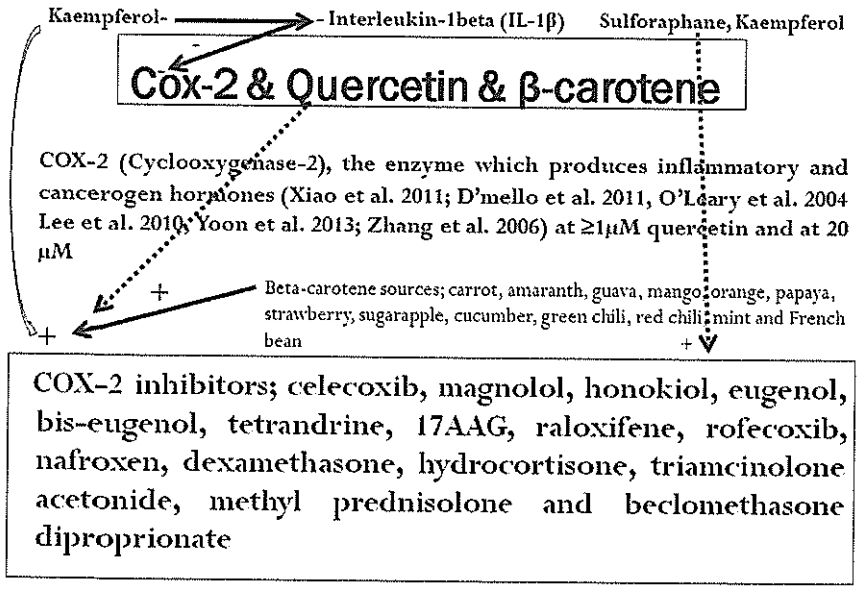


FIGURE 90

The vitamin A rich foods; e. g. collards, cabbage, Brussel sprouts, broccoli, cabbage, apple, banana, peer, avocado, grape, lettuce, mango, melon, okra, onion, orange, red pepper, Japanese persimmons,

raspberries, winter squash, tomato, the vitamin rich foods; e.g. red pepper, orange, green pepper, broccoli, sterawberries, Brussel sprouts, tomato, tomato juice, cabbage, cauliflower, potato, spinach, greenpeas, the vitamin E rich foods; e.g. cauliflower, potato, leek, onion, parsley, cucumber, cod fish, cottage cheese, coconut and the sulforaphane rich foods; e. g. white cabbage, broccoli, red cabbage, cauliflower, Brussel sprouts, radish, mustard, turnip and Chinese kale, the kaempferol rich foods; e.g.broccoli, apple, grape, endive, kale, leek, tomato, cherry, capsicum pepper, parsley, blueberries, celery, apricot, plum, strawberries, herbs; tea, *Ginkgo biloba*, *Sophora japonica*, *Moringa oleifera*, *Tulia* spp.., all together, as combined in anticancer diet, may have a greater anticancer effect since all the mentioned vitamins and flavonoids including kaempferol may form a synergy via the activation of Nrf2 and phase II antioxidant enyzymes.

KAEMPFEROL STUDIES about it's ASSOCIATION with VARIOUS CANCER TYPES

- 183.518 men and women/529 cases of pancreas cancer/8 years of follow up/ 4.53 mg/d (0.58, 1.05-0.014, 95% CI) versus 3.62 mg/d (R:1.00, 95% CI) decreased the risk / smoking adjusted, alcohol not/59-61 years of age (Nöthlings et al. 2007)/Cohort.
- 837 control/ 558 lung cancer/ ≥1.5 mg/d (0.77, 0.54-1.1, 95% CI) versus <0.5 mg/d (R: 1.00, 95% CI) decreased the risk/ smoking adjusted, alcohol adjusted (Cui et al. 2008)/Case.
- 66940 women/215 ovarian cancer/1984-2002/ 30-55 years of age/ 11 mg/d (as the highest quartile)(0.60,0.42-0.87, 95% CI) versus 0.8 mg/d (as the lowest quartile) (R: 1.00, 95% CI) reduced the risk/ smoking adjusted, alcohol adjusted/ 0.8 mg/d (Gateds et al. 2007)/ Cohort.
- 27.111 male smokers /50-69 years of age/19.4 years of follow up/ smoking adjusted, alcohol adjusted/ >1.29 mg/d (0.37, 0.17-0.79, 95% CI) versus ≤0.24 mg/d (R: 1.00, 95% CI) decreased the risk of pancreatic cancer (Bobe et al. 2008)/Cohort.
- 27.062 men and women/6.1 years of follow up/50-69 years of age/alcohol adjusted, smoking adjusted/ 4256 µg/d (0.92, 0.63-1.33, 95% CI) versus 130 µg/d (R: 1.ç00, 95% CI) did not make any change on the risk of renal cell carcinoma (Bertoia et al. 2010)/cohort.
- 206 control/103 lung cancer/63 years of median age/ smoking adjusted, alcohol not/1989-1992/ 1.24 mg/d (0.60, 0.29-1.24, 95% CI) versus 0.34 mg/d (R:1.00, 95% CI) decreased the risk (Garcia-Closas et al. 1998).

BETA CAROTENE

Beta-carotene is one of a number of naturally occurring compounds which are called carotenoids from more than 600 naturally occurring carotenoids, 50 of which have vitamin A activity (Olson and Krinsky 1995; Eldahshan and Singab 2013). These carotenoids absorb high energy for use in photosynthesis and protect chlorophyll from photo-damage (Armstrong and Heart 1996). Carotenoids that contain unsubstituted beta-ionone ring, including beta-caroten, have vitamin A activity and can act as antioxidant. Carotenoids are accumulated in choloroplasts of all green plants as a mixture of alfa- and beta- carotene, B-cryptoxanthin (Delgado-Vargas et al. 2000).

Currently, the only essential function of carotenoids well known is that of provitamin A carotenoids (alfa-carotene, beta-carotene and beta-cryptoxanthin) to serve an a source of vitamin A.

Beta caroten (BCT) has long been regarded as an antioxidant since it is effective in vitro in neutralizing singlet oxygen (O_2) and to a lesser extent, the provitamin interupts lipid peroxidation chain reactions (Paiva and Russell 1999; Paolini et al. 2003).

The polycyclic hydrocarbones which contaminate plants by the means of soil and weather and are often naturally produced in meat and meat product when they are cooked at high temperatures, are metabolically activated in cells by P450 enzymes; CYP1A1/-A2 or peroxidases and reactive intermedates that damage DNA which is crucially important and an initiator point in cancer formation (which is also previously mentioned in 13C part). On the other hand, though the provitamin is an antioxidant, it has also been suggested to be able to stimulate progression of latent tumors (Tanya at al. 2013) which could involve changes in cytochrom P450 enzymes (Paolini et al. 1994). But, this is only a hypothesis and the link between cancer progress and Beta-carotene, claimed by source studies (Dulinska et al. 2005; Paolini et al. 1999) may be due to the induction of P450/CYP enzymes; CYP1A1/2, CYP3A1/2, CYP2E1, CYP2B1/2 and CYP2C11 (Paolini et al. 2001; Liu et al. 2002; Paolini et al. 1999).

The findings of these studies are consistent with the presumption that the polycyclic aromatic hyrocarbones and peroxides in cigarette smoke in rich amounts may increase since they may be converted to ROS by CYP enzymes induced by BCT(β-carotene) if the heavy smoker with or, without cancer take BCT suplements or foods rich in BCT. Thus, it may seem reasonable to assume that the induction of CYPs by BCT could increase ROS more, especially in heavy smokers, with the great amouts of nitrogen dioxide, hydroquinones and peroxy radicals ROS; which are already exist in cigarette smoke (Paolini et al. 1999); Maser 1997; Trustcott 1996 and Blot et al. 1993).

BCT shows its antioxidant behavior only as partial pressures less than 150 torr, the pressure of oxygen in normal air which are exist in most tissues. But, higher oxygen pressures, BCT poses its antioxidant activity and shows an autocatalytic and prooxidant effect, like in the lung surface with the cells with a higher oxygen partial pressure than other tissues (Burton and Ingold 1984).

Benzo(a)pyrene and other polycyclic aromatic hydrocarbons (above 200) are associated with increased risk of colon and rectum adenomas (Since et al 2001; Martinez et al 2007) which may form by high temperature cooking methods (Janoszka et al. 2004). All these findings support the claim which indicates to the necessity for avoidance from done and overdone meat and meat products and their regular consumptions, (as in broiling, frying or grilling above 200 °C), in cancer patients and smokers, since BCT may increase the prooxidants and oxidants which come into the lungs by the means of smoke and well-done meat, meat products and other high-protein foods (e.g. poulty and dairy products..), by inducing CYP ezymes. On the other hand, although there are no studies, beta carotene may worsen the hypoxia in heavy smokers since the antioxidant provitamin binds singlet oxygen in blood in heavy smokers and thus, may create a less-oxygenated environment which triggers the growth of cancer cells (Brown 2007).

The treatments by the anti-cancer drugs which produce ROS and target cancer cells by ROS; sunitinib, sorafenib, tetrandine, cisplatin, bortezomid, vorinostat, MG-132, metformin, thapsigargin, tunicamycin, 17AAG, DBeQ, ritonavir and brefeldin A, may be contraindicated when they are combined with beta carotene supplementation or beta carotene

rich foods like; carrot, amaranth (Gautam et al. 2010), guava, mango, orange, papaya, strawberry, sugarapple, (Charoensiri et al. 2009), cabbage, spinach, tomato, lettuce, cucumber, green chili, red chili, mint and French bean(Ahamad et al. 2007), in smokers with cancer or the smokers with cancer who consume high amounts of well-done cooked high protein foods, especially meat and meat products regularly, since benz(a)yrene and other polycyclic, aromatic hydrocarbons in the foods and meat and meat products, may be converted into ROS by beta caroten which may increase the amount of ROS while inducing the hypoxia in chronic smokers. This may result in cancer cell growth via the hypoxia (a mentioned above in detail). But, if the patient does not have smoking habit, the same pro-vitamin and its rich sources may be advised since they may increase the level of ROS production of the mentioned ROS inducing anticancer drugs.

Briefly, the status of beta-carotene appears very differently and crucial from all other bioflavonoids and antioxidants, because it may be an antioxidant but may also be a prooxidant, depending on smoking and nutrition style of the patient. If the anti-cancer drugs above are administered, tha patient should refrain from both smoking and well-done cooked high-protein foods, especially grilled, broiled and and fried red meat and red meat products.

The extraordinary disadvantage of beta carotene comes into consideration if the patient follows cooked high protein foods like red meat, poultry meat and their products regularly and cannot refrain from smoking. Otherwise, it may be a wrong approach scientifically to make an overall evaluation about the anticancerogenic potantial of the provitamin in cancer nutrition, without analyzing the effects of it on many other parameters in cancer, besides ROS. When the effects of the provitamin on other cancer parameters are concerned, the provitamin appears to induce the activity of caspase (Palozza et al. 2003; Prasad et al. 2006; Wertz et al. 2005; Zhang et al. 2009; Wu et al. 2009.), the apoptotic enzymes which are previosly mentioned in detail, while this induction is also accompained with the decrease of antiapoptotic protein Bcl-2 and the increase in the cleaved from of BID, the protein which permeabilizes the outer mitochondrial membrane, releases cytochrom

c and forms the quaternary protein apoptosome, all contributing to apoptosis.

Since the activation of caspases permeabilizes the mitochondrial membrane and results in the influx of ROS out of the membrane, the same risk and contraindication, mentioned for the patients who smoke and consume cooked high-protein foods regularly, may appear for the anti-cancer drugs which activate caspases; costunolide, cisplatin, mitomycin C, garcinol, brefeldin A, valinomycin, piceatannol, kinetin riboside, lipase inhibitor, THL (tetrahydrolipstatin), imiquimod, SC 560, romidepsin, ouabain, digoxin, proscillaridin A, borrelidin, sanguinarine, bortezomib, MT-21, lonidamine, K858, saikosaponin A, CIL-102 and prodigiosin, leading to extremly high amounts of ROS and thus, extreme damage in both cancer and healthy cells, the ROS which are already exist in smoke or which are converted from the prooxidants which may be exist in cooked high-protein foods. But, if the patient is not a smoker or/and does not consume the cooked high protein foods in high amounts regularly, then the treatments by the mentioned drugs can be administered with much less side effects and contraindication. So, the analyzed risk of BCT and BCT rich foods is only limited to the patients who smoke and who consume cooked and overcooked high protein foods regularly, as in high amounts. This risk should not be generalized to other people.

In spite of the risk of BCT and BCT rich foods on the patients who smoke and/or consume cooked high protein foods regularly in high amounts, when the other anti-cancer effects of the provitamin are analyzed, in the rest of the people without smoking and heavy consumption of cooked high-protein food, one of the effects may be due to the inhibitory effect of the pro-vitamin (20 μM), on COX-2, the enzyme which is responsible for the inflammatory hormones (the anticancerogenic effect of BCT has been observed in *Helicobacter pylori* and some viral infections and in cancer including the ones of colon and stomach) (Palozza et al. 2005; Jang et al. 2009; Lin et al. 2012). Therefore, BCT supplementation or the food consumption rich in BCT (carrot, amaranth, guava, mango, orange, papaya, strawberry, sugarapple, cucumber, green chili, red chili, mint and French bean), may increase the anticancer potential of the drugs; sunitinib, celecoxib,

radidicol, metformin, magnolol, honokiol, eugenol, bis-eugenol, tetrandrine, 17 AAG, raloxifene, rafecoxib, naproxen, dexamethasone, hydrocortisone, triamcinolone acetonide; methyl prednisolone, beclomethasone diproprionate and sorafenib, since these drugs also inhibit COX-2 activity during the treatments, like BCT.

BCT also inactivates ERK 1-2, but as less than alfa carotene. The inhibition of activity of the intracelluar protein/serine/threonine kinases by BCT may be another anticancerogenic effect of the provitamin (Liu et al. 2015).

Thus, the BCT supplementation or the consumption of the foods rich in BCT; carrot, amaranth, guava, mango, orange, papaya, strawberry, sugar apple, cucumber, green chili, red chili, mint and French bean during the treatments by the drugs which inhibit ERK activity like varinostat, ritonavir, radicicol, tamoxifen, geldanamycin, lapatinib, fulvestrant, PD98059, U0126, honokiol, SNX212, may yield greater anti-oxidant potential, since both BCT and the mentioned drugs kill tumors via the inhibition of ERK activity while sulforaphane and sulforaphane rich foods; white cabbage, Brussels sprouts, radish, mustard, broccoli, red cabbage, cauliflower, chinese kale and turnip should be avoided during these treatments since sulforaphane induces ERK activity and these drugs, and thus, may be contraindicated. On the other hand, BCT, unlike sulforaphane, may decrease the side effect stems from the overactivity of ERK caused by; PD98059, gefitinib, cisplatin, sorafenib, paclitaxel, brefeldin, octahedral Pt(IV) complex k101, thapsigargin, bortezomid, metformin, raloxifene, 12-0-tetradecanoyl-phorlol-13-acetate (TPA, thapsigargin and valproic acid combination). Therefore, during the treatments with these drugs, BCT supplementation or the consumption of the foods rich in BCT, may help for a better prognosis via the inhibition of ERK activity, unlike sulforaphane.

The effects of BCT on Grp78, the central regulator of endoplasmic reticulum (ER) function because of its protein folding assembly, and alpha2-macroglobulin which is the activator of GRP78 are still unknown. If the provitamin has inhibitory effect on GRP78 or alpha2-macroglobulin which means the disintegration of the membranes of endoplasmic reticulum of cancer cells, this may be a new target for the novel anti-cancer treatments which are waiting for the urgent studies

to highlight these effects. Smilarly, urgent studies are also needed to search for the effects of the provitamin on G6PDH, the antioxidant which shows overexpression and activity in cancer cells, triggered by IGF-1, antiapoptotic hormone.

The provitamin inhibits the phosphorylation of Akt (serine/threonine-specific protein kinase) while increasing the activity of caspases -3, -7, -8 and -9 (Palozza et al. 2008). Besides, BCT, resveratrol and resveratrol (as previously mentioned in the related part of resveratrol) and I3C and I3C rich foods, curcumin and curcumin rich foods and sulforaphane and sulforaphane rich foods activate the gene, p53 (de Oliveira et al. 2014; Ye et el. 2015 and Choi et al. 2010). Thus, the involvement of the foods rich in these bioflavonoids may also enhance the anti-cancer potential of the provitamin, resveratrol and the mentioned drugs which activate p53. Therefore the anti-cancer effects of the drugs which inhibit Akt, namely; LY29002, SF-1126, NVP-BEZ235, XL147, XL765, ISC-4, GSK690693, MK-2206, fused pyrimidines, phosphatidylinositol (3-5) triphosphate (PIP3), GDC-0941, celecoxib, 7-hydroxystaurosporine (UCN-01), BX-795, BX-912, BX-320, CCT128930, GDC-0068, perifosine, GSK-2141795, GSK2110183, Ipatasertib, Afuresertib, AT13148, PF-04691502, A47867 and Triciribine, may increase if they are administered during beta carotene suppl.and BCT rich foods like; carrot, amaranth, guava, mango, orange, papaya, strawberry, sugar apple, cucumber, green chili, red chili, mint and French bean and also, on previously mentioned in the related part of resveratrol suppl. and resveratrol rich foods like; grapes, blueberries, raspberries and mutberries. Not only resveratrol and BCT but also sulforaphane and sulforaphane rich foods (white cabbage, broccoli, red cabbage, cauliflower, Brussels sprouts, radish, mustard, turnip and Chinese kale), curcumin and curcumin rich foods (cinnamon, cinnamon containing foods and *Curcuma langa*) and I3C and I3C rich foods (cruciferous vegatables. e.g., broccoli, cabbage, cauliflower, bok choy and Brussels sprouts) inhibit Akt, like BCT and resveratrol (Howells et al. 2002; Yu et al. 2008 and Chaudhuri et al. 2007). Thus, the involvement of all the mentioned foods during these drug administrations may enhance their anti-cancer effect due to the synergism with these drugs, the flavons and the provitamin via the inhibition of Akt.

The provitamin's other anti-cancer effect may be via the induction

of caspase activity, cytochnome a release and subsequently ROS influx which triggers the decrease in the antiapoptotic protein Bcl-2 (Palozza et al. 2003; Peng et al. 2010; Prasad et al. 2006). Therefore, the anti-cancer drugs; sunitinib, sorafenib, reolysin, toyocamycin, sangivamycin, tetrandrine, bortezomid, paclitaxel, brefeldin A, sanguinarine, parthenolide, geldanamycin, radicicol, the gene therapies; Apaf1, FADD, Smac/DIABLO, retaspimycin, SNX-2112, daunorubicin, doxorubicin, etoposide, mitomycin, cisplatin, dactinomycin, honokiol and M3-132, may show stronger anti-cancer potential when administered as combined with BCT supplementation or food consumption rich in BCT, inducing caspase activity more with these anti-cancer drugs as mentioned above. Note that, sulforaphane and sulforaphane rich foods like; broccoli, white cabbage, Brussels sprouts, kale and green leafy vegatables, may be added into the combination of these drugs and BCT rich foods and this may even increase the anti-cancer potential of them since sulforaphane also activates caspases.

One anticancerogenic effect of the provitamin may be the inhibition of the expressible of GATA3, the protein which regulates luminal epithelial cell differentiation in the mammary gland, which results in the inhibition of another cancer inducing key receptor, ERalpha. But, there is no any study to highlight this effect for the provitamin currently. Similarly, a possible protection of the genes, BRCA1 and BRCA2, which produce tumor suppressor proteins, against mutations by the provitamin, may be another anti-cancer potential of BCT but, there is also no study currently to claim whether such effect is exist for the provitamin. The androgen receptor (AR), a nuclear receptor that is activated by binding androgenic hormones, which controls the rate of transcription of genetic information from DNA to messenger RNA, may be another anti-cancer pathway of the provitamin. Similarly, whether the alfa-receptor negative prostate cancer cells have the effect of the provitamin on the gene, is currently not studied. The inhibition of sphingosine kinase 1 (SphK1) which catalyzes the phosphorylation of sphingosine to SIP, siphingosine-1-phosphate, a sphingolipid to induce cell growth and apoptosis, may be another anticancerogenic effect of the provitamin but there is currently no study which highlights such effect. One of the most effective anti-cancer pathways; the Hedgehog

signaling, which transfers information to embryonic cells for the proper cell growth during BCT supplementation and the relation between the provitamin and signaling have not currently been highlighted. The question of the possible inhibitory effect of the pro-vitamin on the expression of E2F3 gene, which cooperates with the removal of the retinoblastoma protein (pRB) supressor control at the G1/S transition in the cell cycle, is still waiting to be answered. Similarly, whether BCT inhibits the antioxidant gene, G6POH, which is overexpressed and overactivated in cancer cells has not currently been studied.

FOXO3, the gene which is a transcription factor and which triggers apoptosis through upregulation of other genes, required for the cell death, like Bim and PUMA, may be another anti-cancer pathway of BCT. The provitamin attenuates the H_20_2-induced nuclear localization of FOXO3a which improves and induces FOXO3 activity, making it free (Ogawa et al. 2013).

The activation of FOXO3 has also been claimed by the same autors to attenuate muscle loss which may make the involvement of the provitamin into cancer diet necessary to slow and protect muscle loss in cancer patients.

The anti-cancer drugs which induce FOXO3; metformin (Aldea et al. 2014; Sun et al. 2012); doxorubicin (Hui et al. 2008); nipradilol, timolol (Miyamoto et al. 2009); melatonin (Carbajo- Pescador 2013); withaferin A (Stan et al. 2008); bortezomib (Dewar et al. 2012); Vorinostat (Shats et al. 2013); tunicamycin (Ghosh et al. 2012); paclitaxel (Sunters et al. 2006); geldanamycin (Karkoulis et al. 2013); AZD5363 (Fox et al. 2006); cisplatin (de Mattos et al. 2008) and S-aza-2-deoxycytidine (Geiger et al. 2012), the anti-cancer drugs whose inducing effect on FOXO3 was confirmed by the authors in the paranthesis) may show stronger anticancerogenic effect if these drugs are administered as combined with beta carotene rich foods; guava, mango, orange, papaya, strawberry, supar apple, cucumber, green chili, red chili, mint and French bean. Also peanuts, grapes, blueberries rich in resveratrol which induces FOXO3 (on mentioned previously in the related part) and white cabbage, broccoli, red cabbage, cauliflower, Brussels sprouts, radish, mustard, turnip and Chinese kale rich in sulforaphane, since sulforaphane and resveratrol, like BCT, induce FOXO3 (Davis et al. 2009).

THE COHORTS about the ASSOCIATION of 'BETA CAROTENE and CANCER'

- 5681 women / 155 cancer / 40-59 years of age / 1980-1993 / smoking adjusted, alcohol adjusted/6823.5 μg/d (1.40, 0.76-2.59, 95% CI) versus 3152.2 μg/d (1.78, 1.04-3.05, 95% CI) had no effect on the risk of lung cancer (Rohan et al. 2002).
- 29584 men and women / 40-69 years of age / 1986-1991 / 147 lung cancer / smoking adjusted, alcohol adjusted / daily beta carotene supplementation (0.55, 0.26-2.14, 95% CI) reduced the risk in 31 lung cancer, versus no supplementation (R:1.00, 95% CI) (but, the amount of the supplementation is not mentioned in the published paper) (Kamangar et al. 2006).
- 18314 men and women / 6.2 years of follow-up / Smoking adjusted, asbestos adjusted, alcohol adjusted / 30 mg beta carotene and 25000 IU retinyl palmitate (vitamin A) combination (6.2, 4.8-7.9, 95% CI) versus no supplementation (4.1, 2.7-6.3, 95% CI) did increase the risk of lung cancer in smokers!!! (Omenn et al. 1996). These results are highly consistent with the ones of the Alpha-Tocopherol Beta-Carotene Cancer Prevention Study Group, involving 29133 male smokers in Finland with 20 mg/d beta carotene supplementation (0.17, 0.10-0.29, 95% CI) versus no supplementation (R:1.00, 95% CI) during 8 years as smoking and alcohol adjusted. They also found no effect. So, all these results indicate to a possible increasing risk of lung cancer with beta-carotene and/or any other pro-vitamin A if they are supplied as combined with smoking!!!).
- 59910 women / 40-65 years of age / 7.4 years of follow up / smoking adjusted, alcohol adjusted / 3 times beta carotene supplement intake / week (2.14, 1.16-3.97, 95% CI) as the highest quartile versus the lowest (R:1.00, 95% CI) decreased the risk of tobacco related cancers (Touvier et al. 2005).
- 1378 men and women/5.4 years of follow up / smoking adjusted, alcohol adjusted / <2.5 μmol/L total plasma concentration as the

lowest quartile (R:1.00, 95% CI) as compared with the highest (35.9, 8.1-63.7, 95% CI) did not make any change on the rate of asbestos related diseases including cancer (Alfanso et al. 2005).

- 29133 men / 50-69 years of age / 126 gastric cancer / 1985-1993 / 20 mg/d beta carotene supplementation (0.88-1.80, 95% CI) versus no supplementation (R:1.00, 95% CI) (Malila et al. 2002).
- 27084 male smokers / 50-69 years of age / 1644 lung cancer / 14 years of follow up / smoking adjusted, alcohol adjusted / >290 μg/L beta carotene in take as the highest quartile (0.81, 0.69-0.95% CI) versus >99 μg/L as the lowest (R:1.00, 95% CI) decreased the risk of lung cancer (Holick et al. 2002).
- 1059 lung cancer / 27111 men / 7.7 years of follow up / smoking adjusted, alcohol adjusted / 2199 μg / d beta carotene intake as the highest quartile (0.8,-1.2, 1.00, 95% CI) versus 1981 μg/d as the lowest did not make any change (Woodson et al. 1999).
- 106 epidermoid lung cancer / 212 controls / 1983-1984 / Smoking adjusted, alcohol adjusted / <50-80< years of age / 7226 IU/d as the highest quartile of beta carotene versus the lowest, 5028 IU/d (R:1.00, 95% CI) decreased the risk of lung cancer (Dartigues et al. 1990).
- 29105 men / 24 years of follow up / smoking adjusted, alcohol adjusted / 50-69 years of age / 20 mg/d beta carotene supplementation (1.13, 0.86-1.49, 95% CI) versus no supplementation (R:1.00, 95% CI) did not make any effect (Lai et al. 2014).
- 32826 women / 2188 breast cancer / 43-69 years of age / 20 years of follow up / smoking adjusted, alcohol adjusted / ≥419 μg/dL serum beta carotene as the highest quartile (0.74, 0.60-0.91, 95% CI) versus <136 μg/dL as the lowest (R:1.00, 95% CI) decreased the risk (Eliassen et al. 2015).
- 62573 women / 650 breast cancer / 55-69 years of age / 4.3 years of follow up / 0.719 mg/d as the highest (1.01, 0.72-1.42, 95% CI) versus the lowest quartile, 0.197 mg/d (R:1.00, 95% CI) did not make any change on breast cancer (alcohol adjusted, smoking not (Verhoeven et al. 1997).

- 121700 women/969 breast cancer/30-55 years of age / 1980-1998 / smoking adjusted, alcohol adjusted / 1.15 μmol/L (0.53-1.02, 0.73, 95% CI) versus 1.03 μmol/L as the lowest (R:1.00, 95% CI) decreased the risk (Tamimi et al. 2005).

According to the mentioned cohorts, beta carotene may have a beneficial anticancer potential. The most significant and unexpected point about the provitamin and its association with cancer are the cancer stimulating effect of the provitamin rather than being anticancerogen in smokers!!. The main possible explanation may be due to the Reactive Oxygen Species (ROS). As they have often been mentioned in many parts, these substances have dual effect. If they are taken into body or produced in body in excess amounts by the means of smoking, alcohol, asbestos, the chemicals in air, the foods rich in fat and sugar and finally and probably as one of the most important contributors, stress, then they can accumulate around the cytoplasmic membrane of healthy cells, damage them which may lead to the partial cell wounds or deaths, forming organ or tissue deficiencies. Excess of these radicals may be the precursors of some cancerogenic substances. They may degrade the mocosa layers of gastrointestinal tract, leading to ulcer and gastritis. They may accumulate on the surface of intima layers of blood vessels and thus, may be responsible for the progress of atherosclerosis (vessel calcification). The atherosclerosis due to the excess amount of ROS production may take place in all parts of the vessel from coronary to brain vessels. Therefore, the same chemicals may form Alzheimer, Parkinson, stroke or hearth failure. Briefly, fatty, candy and processed foods, the foods in simple carbohydrates (poor in fiber) may always lead to one or some of these diseases by forming too much ROS production. On the other hand, though they have got harmful effects in healthy metabolisms, their mentioned harmful effects have been exploited in some cancer treatments, which appears as one of the novel anticancer treatment approaches, based on the destruction of cancer cells with a great number of ROS in addition to the ROS produced by some anticancer drugs. Such synergisms were often mentioned in many parts of the book, the synergisms which kill cancer cells by ROS, produced by food and drug as combined. But, the same approach should be evaluated

very differently when it comes to smokers since smoke enters many ROS into body. Beta carotene supplementation or beta carotene rich food consumption in smokers causes to much ROS production, like smoking. As a result, these greater amounts of ROS may be converted into some cancerogenic substances while these substances can mutate the genom of the cell, leading cancer. Therefore, although beta carotene seems to have some anticancerogen potential, in contrast, it may cause cancer in smokers via the mentioned mechanism of ROS. Another reason may be the Oxygen scavenging attribute of BTC. BTC takes single O atom during its antioxidant effect like nicotin does. Their combined effect may create a much more hypoxic media which attract cancer cells, leading to their growth.

n-3 Omega Fatty acids and their association with overall health and cancer

The very long chain polyunsaturated fatty acids (PUFAs) (C18–C22) and n-3 Omega PUFAs are apparently widely accepted as a part of modern nutrition because of their beneficial effects on metabolism. Most significantly, the reported protective effect of the n-3 omega fatty acids in relation to cardiovascular inflammatory diseases and cancer has led people to consider these fatty acids more beneficial than other dietary supplements. Unfortunately, there is a lack of studies relating to the physical performance increasing effect in sports diets, cholesterol-reducing effect in meat technology, effects on human serum profile, the application dose and the side effects with/without omega-6 PUFAs, which has left us with several crucial unanswered questions. We still do not know the correct dose of n-3 omega and the correct ratio of n-3 omega to n-6 omega or their possible contraindications when combined with drugs, other foods and herbal supplements. Another reported aspect of n-3 omega PUFAs is that they protect and even enhance the effect in medical treatment of important diseases such as Alzheimer's, multiple sclerosis and cancer. These reports led to PUFAs becoming one of the most accepted and consumed food supplements. Despite this weight of evidence and the considerable current use, there is still a need for studies, which will determine whether the n-3 omega fatty acids are in fact important functional supplements with no adverse effects. This review will attempt to outline the current position of n-3 omega fatty acids in the field of clinical nutrition and healthcare and outline the studies needed to determine whether there are significant advantages in taking them as food supplement without any adverse effects.

n-3 Omega polyunsaturated fatty acids (PUFAs) are long chain PUFAs found in plants and marine sources such as fish, mussel, oyster, shrimp but primarily cold water fish (Friedman and Moe, 2006), but also exist in a wide range of plant products such as nuts, especially English walnuts, seeds, namely sesame (Namiki, 2007), flax seed and vegetable oils such as soybean and canola besides olive (Whelan and

Rust, 2006). n-3 Omega fatty acids, unlike saturated fatty acids, have been associated with various health benefits relating to treatment of rheumatoid arthritis (Rennie *et al.*, 2003) and coronary artery disease (Freeman, 2000) whilst improving blood pressure control and preserve renal function even in hypertensive heart transplant recipients (Holm *et al.*, 2001). The effects of n-3 omega PUFAs on various cancers and also on other clinical disorders including oedema, rheumatoid arthritis, cardiovascular disease and others, is closely related to their metabolism. Hence replacement of saturated fat with unsaturated fatty acids for the protection against metabolic diseases and disorders, n-3 omega PUFAs have been widely accepted as one of the cornerstones of healthy lifestyle and nutrition.

Identification of PUFAs

The very long chain PUFAs (C18, C20 and C22) include the two essential fatty acids; linoleic acid (LA) [18:2 (n-6 omega)] and α-linolenic acid (α-LN) [18:3 (n-3 omega)] and are most commonly found in large amounts in some certain fish species (Poisson, 1990). These two essential fatty acids (EFAs) are the only sources for the production of important longer chain PUFAs such as prostaglandins; dynamic but short lived compounds that control blood vessels and other body functions. Arachidonic acid (AA) (20:4 n-6) (Pereira *et al.*, 2004), a member of the n-6 PUFA, is another source of prostaglandins (PG). Eicosapentaenoic acid (EPA) (20:5 n-3), LN and docosahexaenoic acid (DHA) (C22) EFAs are called three PUFAs or n-3 omega PUFAs (n-3 series) (Pereira *et al.*, 2004). In addition, dietary LN can be converted to the EPA and DHA. AA, LN and LA, long chain and highly unsaturated fatty acids are truly essential, while C18 compounds, stearic and palmitic acids, abundant in animal fat, should be considered as conditionally essential (Trautwein, 2001).

Metabolic pathways of n-3 omega PUFAs

Consumption of lipid emulsions rich in omega 6 PUFAs (LA and AA) leads to an increased amount of dienoic prostaglandin E2 (PGE2) (a group of hormone -like substances that participate in a wide range of bodily functions such as contraction and relaxation of smooth muscles, dilation and constriction of blood vessels, control of blood pressure and modulation of inflammation), thromboxane (a lipid which constricts blood vessels and is produced in platelets) and leukotriene (a lipid responsible for the effects of inflammatory response by the production of histamine) production as a result of the metabolic breakdown of AA. PGE2 production from AA is catalysed by a key membrane-bound enzyme, Prostaglandin endoperoxidase synthase (Pghs). Thromboxane A2, which is produced by Pghs2, is responsible for vascular permeability, platelet aggregation and oedema (Kramer *et al.*, 1996; Tapiero*et al.*, 2002). PGE2, thromboxanes (especially thromboxane A2) and leukotrienes are responsible for their immunosuppressive properties and for the generation of free oxygen radicals. Briefly, inflammation and thrombogenesis rates are mainly controlled by n-6 PUFAs (LA and AA). In contrast, emulsions rich in EPA, LN and DHA (n-3 omega PUFAs) inhibit the breakdown of AA, which is produced by the synthesis of PGE2 (Fig. 1). This group (LN and dihomo α-LN) produces PGE1, a hormone in lipid origin which has got beneficial effects on the body, opposite to those of PGE2, such as regulation of calcium movement, controlling hormone regulation and cell growth, PGE3 and PGI3. PGE3 and PGI3 have got beneficial effects similar to those of PGE1, such as inhibiting inflammation and increasing trienoic PGs, thromboxane A3 and pentaenoic leukotrienes (e.g. LTB5) (Trautwein, 2001). PGD2, a prostaglandin which is only found in the brain and mast cells, is critical to the development of allergic diseases and is involved in the regulation of reducing body temperature, in sleep, acts as an opposite to PGE2. But, PGE2, produced by n-6 omega PUFAs, has an awakening effect (Yehuda et al. 1999). PGE1, E3 and I3 inhibit the inflammatory reactions, as opposed to PGE2, while thromboxane A3 decreases

platelet activation and thrombogenesis rate as opposed to thromboxane A2 which is produced by n-6 omega PUFAs. Simply stated, n-3 omega PUFAs lower the risk of inflammation and thrombogenesis caused by n-6 omega PUFAs (Nitenberg and Raynard, 2000). Dietary LN is rapidly converted to another n-3 omega (dihomo α-LN), which can then be converted to n-6 AA.

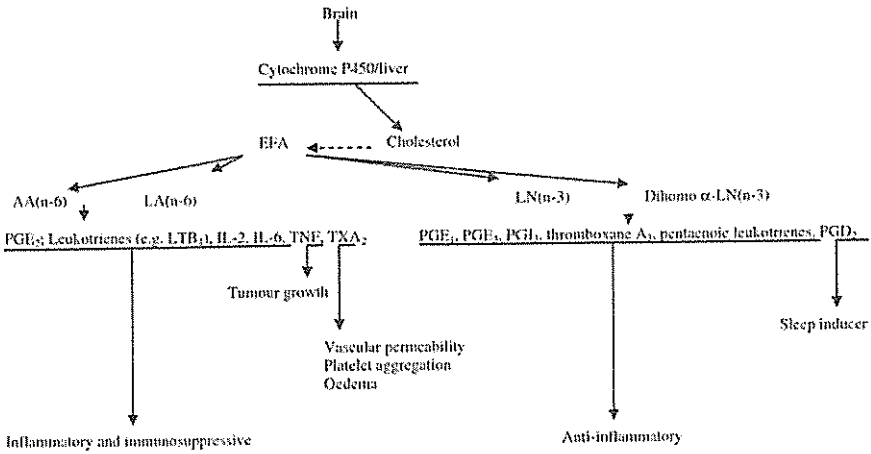


FIGURE 91

Since AA is the precursor of the inflammatory agents such as PGE2, cytokines, interleukin-1 (IL-1), interleukin-2 (IL-2), interleukin-6 (IL-6) and dihomo α-LN is the precursor of the anti-inflammatory 1-series eicosanoids such as PGE1 (Endres et al., 1989; Yehuda et al., 1999), it is not only the ratio of AA to dihomo α-LN or LN, but also the conversion rate of these fatty acids to each other, which is the significant factor in predicting whether there will be inflammation in the future (Belluzzi, 2001). Dihomo α-LN and LN (as n-3 omega PUFA) also inhibit inflammation by reducing the production of inflammatory PGE2, leukotriene B4 (LTB4), IL-1, IL-2 and IL-6 (Santoli et al., 1990; Baker et al., 2005).

The association of n-3 omega PUFAs with diseases

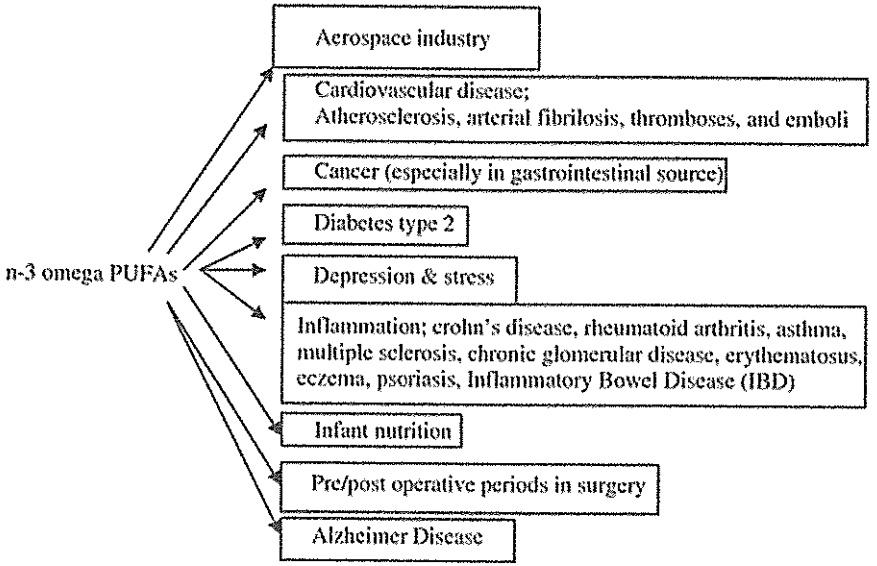


FIGURE 92

Linolenic acid (LN) and palmitic acid contents (g 100 g^{-1}) of some foods.

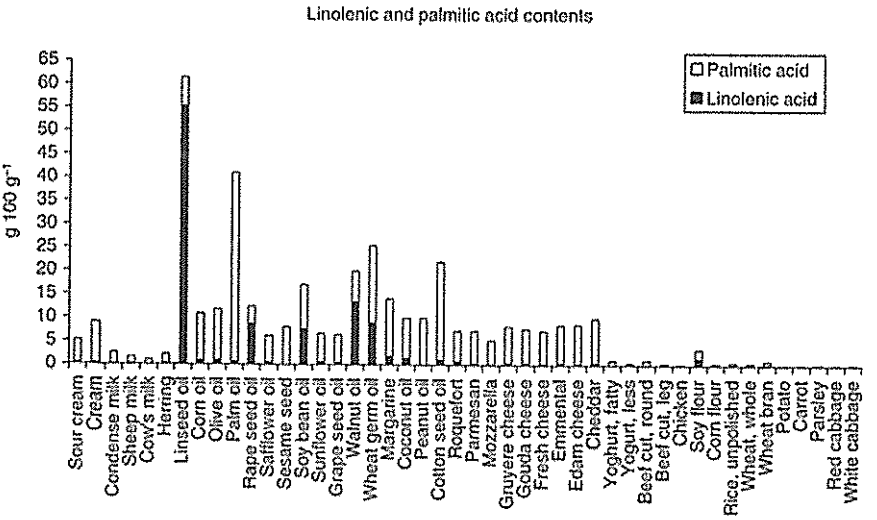


FIGURE 93

The anti-inflammatory properties of n-3 omega PUFAs are used in the treatment of inflammatory diseases such as inflammatory bowel disease (IBD), eczema, psoriasis and rheumatoid arthritis (Cleland et al., 2003). Similarly, an increase in n-6 omega PUFAs and a decrease in n-3 omega PUFAs raises the rate of occurrence of Crohn's disease (inflammation of colon). Inhibition of the proinflammatory cytokine (proteins, peptides or glycoproteins that are produced widely by cells throughout the body cells which are critical to the development and functioning of the immune response by activating immune cells to increase the systems response to the pathogen) synthesis by n-3 omega PUFAs can therefore be beneficially used in the treatment of Crohn's disease (Griffiths, 1998). Treatment of such diseases with n-3 omega PUFAs also reduces mucosal damage caused by inflammation or by Crohn's disease. Stenson et al. (1992) and Hawthorne et al. (1992) have treated ulcerative colitis with first 5.4 g and then 4.5 g of n-3 omega PUFAs (fish oil) and observed significant healing of the colon mucosa. The effects of leukotrienes which are proinflammatory mediators which can lead to post-traumatic immune dysregulation, can also be mediated by n-3 omega PUFA supplementation in the postoperative period. Thus, n-3 omega PUFAs are important anti-inflammatory agents in the postoperative periods (Köller et al. 2003). Additionally, n-3 omega PUFAs, DHA and EPA, were found as to have different in the effects on leucocyte functions such as phagocytosis, chemotactic response and cytokine production. For example, DHA has got an increasing effect in neutrophil proliferation and monocyte phogocytosis while EPA does not have got the same effect (Gorjao et al. 2009).

The supplementation of the standard diet with key nutrients which have immunomodulatory properties such as arginine, omega 3 fatty acids and glutamine (the most abundant non-essential amino acid in body) control the surgery-induced immunosuppression and hyperinflammation effectively (Gianotti *et al.*, 2003). The administration of n-3 omega PUFAs ameliorates the host defence mechanisms, controlling the inflammatory response, not only in postoperative but also in the preoperative periods (Braga et al. 1998). Chen and Yeh (2003) reviewed the beneficial effects of administering by injection of omega 3, in the form of fish oil and indicated the importance of these effects. They

showed that incorporation of the omega 3 into the cellular membranes of many cell populations can consequently influence the disease process, lead to a decrease in platelet aggregation and thrombosis or ameliorate the disease process in certain conditions and reduce accumulation of lipid peroxidation products in liver. Confirming these findings, DHA and EPA were found to serve as substrate for the production of the anti-inflammatory compounds such as resolvins and protectins while inhibiting the activation of nuclear factors that induce inflammation (nuclear factor kappa B and interleukins) (Goldberg and Katz, 2007). The meta-analysis made by them to examine the pain relieving effects of EPA/DHA in patients with rheumatoid arthritis or joint pain secondary to inflammatory bowel disease or dysmenorrhoea (severe uterine pain during menstruation) supports the premise that n-3 omega PUFAs (EPA and DHA) may decrease the pain experience in the patients.

Cardiovascular diseases and n-3 omega PUFAs

Besides the anti-inflammatory effect of n-3 omega PUFAs, the other beneficial and protective effect of these fatty acids is on the cardiovascular system. Trans fatty acids, cholesterol and saturated fats are mainly responsible for atherosclerosis. On the contrary, n-3 omega PUFAs are beneficial in reducing cholesterol and thus the risk of myocardial infarction (Zyriax and Windler, 2000). Another cause of cardiovascular disease formation is the hypertriglyceridaemia, an increase in the serum triglyceride in blood serum level, can also be reduced by the addition of n-3 omega (fish oil) to the diet (Hau et al. 1996). The modern sciences of dietetics and nutrition studies the relationship between nutrition and health so that people can protect themselves from diseases or ameliorate the adverse effects of these diseases by means of appropriate diets (Table 1). The many close relationships between 'a high selenium intake and a lower incidence rate of cancer' (Borek, 2004; Diwadkar-Navsariwaka and Diamond, 2004; Jacobs et al. 2004; Charalabopoulos et al. 2006) despite conflicting evidence of no effect (Clark et al. 1996), 'high carotenoid intakes and lower risk of cancer' (Mannisto et al. 2004), 'dietary fat, high amounts of animal, saturated and trans fat intakes and obesity' (Bray and Popkin, 1998; Field et al. 2007), 'high dietary sodium intake and increase in the risk of hypertension' (de Wardener et al. 2004; Adrogue and Madias, 2007), 'high alcohol intake and stroke risk' (Reynolds, 2003) have been proven and similarly the close link between omega 3 PUFAs and cardiovascular disease is now widely accepted (Temple, 2002). According to Harris et al. (2003), of all known dietary factors, long-chain omega 3 fatty acids may be the most protective against death from coronary heart disease (CHD), by increasing the n-3 omega intake of an individual with coronary artery disease by approximately 1 g/d. The best prevention of cardiovascular diseases appears to be achieved by replacing saturated fats with n-3 omega PUFAs (Temple, 1996). Such replacement appears to have a direct effect on the intrinsic ability of a cardiac muscle fibre to contract at a given

fibre length. These effects indicate to the beneficial and protective effects of omega 3 fatty acids in preventing sudden death following myocardial infection (Bhatnagar and Durrington, 2003). Eicosanoid synthesis from n-3 omega PUFAs minimises the production of PGE2 and thromboxane A2, IL-1, IL-2 and IL-6. Specifically, minimising the production of thromboxane A2 and IL-1, IL-2 and IL-6 by n-3 omega PUFAs protects the individual's health by protecting cardiac tissue from clot formation, platelet aggregation and thrombosis risk (Arkhipenko and Sazantova, Arkhipenko and Sazontova, 1995; Wahlqvist, 1998). A further benefit for the cardiovascular system is the lowering of total cholesterol by n-3 omega PUFAs (Kusunoki et al. 2003). Indeed, daily supplementations of 3 g in men and EPA containing soy phospholipid at 10% level in rat can decrease total serum cholesterol and LDL (bad cholesterol, which sticks free cholesterol in blood onto the walls of blood vessels) whilst slightly increasing high density lipoprotein (Lox, 1990) (HDL: good cholesterol, which is claimed as protective against hypertension and calcification since it can take bound cholesterol from the walls of vessels and return it to blood stream). Supportive data is found in a study in rats in which a soybean oil containing 5% EPA showed a significant decrease in serum triglyceride (TG) levels (Dasgupta and Bhattacharyya, 2007).

The list of PUFAs

Name	Lipid name	Chemical name
Source: Lands (1992).		
α-Linolenic acid (α-LN)	18:3 (n-3)	all-*cis*-9,12,15-ortadacatrienoic acid
Stearidonic acid (STD)	18:4 (n-3)	all-*cis*-6,9,12,15-octadecatetraenoic acid
Eicosatrienoic acid (ETE)	20:3 (n-3)	all-*cis*-11,14,17-eicosatrienoic acid
Eicosatetraenoic acid (ETA)	20:4 (n-3)	all-*cis*-8,11,14,17-eicosatetraenoic acid
Eicosapentaenoic acid (EPA)	20:5 (n-3)	all-*cis*-5,8,11,14,17-eicosapentaenoic acid
Docosapentaenoic acid (DPA)	22:5 (n-3)	all-*cis*-7,10,13,16,19-docosapentaenoic acid
Docosahexaenoic acid (DHA)	22:6 (n-3)	all-*cis*-4,7,10,13,16,19-docosahexaenoic acid
Tetracosapentaenoic acid	24:5 (n-3)	all-*cis*-9,12,15,18,21-docosahexaenoic acid
Tetracosahexaenoic acid	24:6 (n-3)	all-*cis*-6,9,12,15,18,21-tetracosenoic acid

FIGURE 94

Amounts (g) of some foods which should be consumed to provide 1 g EPA and DHA

Fish/sea food	g/d to provide 1 g EPA and DHA per day
Source: Ward and Singh (2005).	
Fresh tuna	70–360
Sardines	60–90
Salmon	60–135
Mackerel	60–250
Herring	45–60
Rainbow trout	90–105
Halibut	90–225
Cod	375–750
Haddock	450
Catfish	450–600
Flounder	210
Oyster (Pacific/eastern/farmed)	75/195/240
Lobster	225
Crab, Alaska King	255
Shrimp	330
Clam	375
Scallop	525

FIGURE 95

Fat content/EPA + DHA (g/ 100 g) and fat content/α-linolenic acid (g/ 100 g) ratio of some various fish, marine products, vegetables and oils

	Fat content (g /100 g)	EPA + DHA (g /100 g)	Fat content (EPA + DHA) (g /100 g)
Eel	24.5	0.83	29.51
Hering	17.8	2.72	6.54
Sprat	16.6	3.23	5.14
Tuna	15.5	3.37	4.60
Salmon	13.6	2.86	4.76
Mackerel	11.9	1.75	6.8
Carp	4.8	0.30	16
Sardine	4.5	1.39	3.24*
Swordfish	4.4	1.79	2.45*
Trout	2.7	0.59	4.58
Halibut	1.7	0.51	3.33*
Cod	0.6	0.18	3.33*
Haddock	0.6	0.16	3.75*
Lobster	1.9	0.20	9.5
Shrimp	1.4	0.30	4.66
Mussels	1.4	0.15	9.33
Anchovy	2.3	0.50	4.60
Sardine	13.9	2.44	

FIGURE 96

	α-LN (g/ 100 g)	Fat content/α-LN (g/ 100 g)
Butter	1.20	69.3
Lard	0.98	102.04
Linseed oil	54.2	1.84
Soybean oil	7.70	12.98
Rapseed oil	9.15	10.93
Walnut oil	13.5	7.40*
Olive oil	0.86	625
Vegetable oil	2.40	33.3
Almonds	0.26	208.07
Hazelnut	0.15	410.6
Walnuts	6.80	9.19
Kale	0.35	2.57*
Lettuce	0.07	3.14*
Parsley	0.12	3.00*
Potato	0.02	5.5*
Cauliflower	0.10	1.8*
Spinach	0.13	2.31*
White cabbage	0.09	2.22*

FIGURE 97

Although most studies define n-3 omega PUFAs as lowering cholesterol and LDL as reducers, a few studies suggest that long term use of n-3 omega PUFAs results in increase in LDL. Schacky et al. (1999) found a 7% increase in LDL, following a period of 2 years during which subjects consumed 3 g of EPA and DHA daily. Similarly, 3 g-7 kg 7/ d use of EPA and DHA, was shown to lower the amount of VLDL (Very Low Density Lipoprotein, which is claimed as more harmful than LDL because of its greater ability to bind free cholesterol on to the

walls of blood vessels), while enhancing the production rate of LDL. The decrease in VLDL and increase in LDL seem to be due to the conversion of VLDL to LDL by postheparin lipase, an enzyme of the hydrolase class which shows its activity in the endothelial surface in mammary, muscle and adipose tissues and is activated by n-3 omega PUFAs (Lu et al. 1999). However, despite this increase of LDL, Schacky et al. (1999) found a slight mitigation of the progress of atherosclerosis. The cholesterol reducing and HDL increasing effect of n-3 omega PUFAs makes them one of the most effective substances in the prevention of atherosclerosis, comparable to niacin, statins, and fibres (Barbeau et al. 1997; Rader, 2003). n-3 Omega PUFA supplementation of the diet has also been seen to lower the blood pressure in rats (Yahia et al. 2003). Similarly, n-3 omega rich rapeseed oil supplementation also has a reducing effect on cholesterol and the ratio of LDL to HDL (Eder and Brandsch, 2002). Li (2003) has supported these findings by confirming the beneficial effects of these fatty acids on systolic and diastolic blood pressure and stroke. This beneficial effect of n-3 omega PUFAs has attracted the attention of humanity in this new millennium and appropriately, the aeronautical industry is employing PUFAs to protect the cardiovascular systems of astronauts against the abnormal and extraordinary oxidative stress of space (Turner et al. 2002).

The protective effect of n-3 omega PUFAs on the cardiovascular system, can easily be increased by niacin, bile acid, resins, sport and exercise, which highlights the importance of life style and nutrition on health. Similarly, increased intakes of marine n-3 omega PUFAs can result in decreased triglycerides, fibrinogen and platelet aggregation, which are considered to be beneficial for cardiovascular diseases (Wijendran and Hayes, 2004). It was found in a study by Sweeney et al. (1999) that Japanese students who had relocated to USA showed higher serum triglyceride, cholesterol levels and a high risk of cardiovascular diseases when compared with the general population of Japan. The apparent explanation of this difference is that the native Japanese diet is high in n 3-omega PUFAs whilst the American diet is not. The fact that higher serum triglyceride, cholesterol levels and high risk of cardiovascular diseases found in Japanese students, following their moving to the USA, can be compared with the lower triglyceride and

cholesterol levels of the general population of Japan, is a clear example, showing the significance of n-3 omega fatty acids as cardio protectors (Sweeney et al. 1999). Liu et al.(2001) added n-3 omega PUFAs to bread, as one of the most commonly consumed food products and this enrichment lowered serum triglyceride level and also total serum cholesterol by increasing HDL. Russo (2009) recommends the intake of 1 g/d of EPA and DHA for treatment of post Myocardial Infarction (MI) and prevention of sudden cardiac death and other cardiovascular dysfunctions. n-3 Omega PUFAs also inhibit protein kinase C and increase in nitrous oxide (NO) release, which inhibits platelet adherence to the collagen and thus eases blood circulation (Schoene, 2001; El-seweidy et al.2002). Thus, supplementation of the diet with n-3 omega PUFAs is very effective and protective against cardiovascular diseases, such as hypertension and atherosclerosis (Shoda et al. 1996; Temple, 2002) and even in the reduction of the incidence of sudden cardiac death (Villa et al. 2002). n-3 Omega supplementation of the diet of rats, decreased the mortality rate, caused by myocardial infarction (MI) while decreasing creatine phosphokinase as the indicator for MI. In contrast, an increased mortality rate was observed when the rat diets were supplemented by saturated fat from coconut oil (Nageswari et al. 1999). Mente et al. (2009) conducted a systematic search of Medline for cohort studies on randomised trials investigating dietary exposures in relation to CHD. They pointed to the moderate evidence of associations that exists for intake of fish, marine n-3 omega PUFAs, folate, whole grains, dietary vitamins E and C, beta carotene, alcohol, fruit and fibre.

Although there is important evidence relating to the protective effects of n-3 omega PUFAs on cardiovascular health, very surprisingly, these fatty acids may accelerate heart beat, cause adverse effects and even be life threatening according to the findings of Raitt et al. (2005). In their randomised controlled trial involving 200 patients, 1.8 g daily fish oil supplementation caused significantly important accelerations of the heart beat in patients with ventricular tachycardia (VT), an accelerated heart beat initiated within the ventricules that may prevent heart from pumping enough blood and ventricular fibrillation (VF), a heart failure due to sudden cardiac death. The findings are seriously important since it indicates that patients with VF and VT should rather avoid n-3 omega

PUFAs. When 37.393 deaths in only USA in 2002 with 1.6% of all deaths that year with $2.2 billion payment to medicare beneficiaries for cardiac dysrhythmias concerned, findings are seriously important and needs further studies for definiteness.

Inuit peoples have a substantially lower rate of acute myocardial infarction, commonly known as a heart attack which occurs when blood supply to heart is interrupted causing some heart cells to die, when compared with Western people despite having a diet high in fats. Studies (Bang et al. 1971; Kromann and Green, 1980) have shown that the diet is high in omega-3 polyunsaturated fats (PUFAs) from sea mammals and fish has a protective effect. In one study, which obtained information on deaths from different diseases for 2005 from US National Center for Health Statistics, Danaei et al. (2009) examined lifestyle and metabolic risk factors in death and determined a deficiency of n-3 omega PUFAs as the eighth highest killer in death for people living in USA. Deficiency of n-3 omega PUFAs with 84 000 death $year^{-1}$ even beat out nutrition rich in trans fat with 82 000 deaths annually as a causative factor. The same study findings also suggested that the huge number of annual deaths (84 000/year) in USA is mainly depended on deficiency of n-3 Omega PUFAs, EPA/DHA, which can also be prevented by omega 3 supplementation and a change in nutrition style to a diet rich in n-3 omega PUFAs. Thus, the study indicates to the importance of increasing consumer awareness of the dangers of about the drastic deficiency of n-3 omega PUFAs. A recent meta-analysis of randomised controlled studies of omega-3 fatty acid supplementation of the diet by Preiss and Sattar (2009) confirmed that this treatment had a cardiovascular benefit but suggested that more data would be needed to support use in clinical practice. With our present data mentioned above, we can note this cardio protective effect of n-3 omega PUFAs. However according to Lee and Lip (2003), the use of n-3 omega PUFAs should be considered as a part of comprehensive secondary prevention strategy in patients following myocardial infarction. It has also been proposed that ischemia-induced arrhythmias may be prevented by n-3 PUFA supplementation (Leaf et al. 2003). In spite of many studies, indicating the protective effect of n-3 omega PUFAs on cardiovascular system, the minimum dose which shows this effect, was not established until the studies by Weber and

Raederstorff (2000). They stated that, 1 g/d n-3 omega (in the form of fish oil) is sufficient to show this serum triglyceride and LDL lowering effect whilst a daily intake of 3 g of EPA and DHA is regarded as safe by Food and Drug Administration (O'Keefe and Harris, 2000). Similarly, Retterstol et al. (1996) claimed the serum triglyceride and LDL lowering effect of n-3 omega, but as combined with drugs to treat hypercholesterolemia. On the other hand, an insufficiency of n-3 omega PUFAs and high amounts of n-6 omega PUFAs may also increase the atherogenic effects of environmental chemicals such as polychlorinated biphenyls (PCB), leading to dysfunction of the vascular endothelium. In spite of the cardiovascular protective effects of n-3 omega PUFAs, n-6 omega PUFAs do not appear to be correlated with cardiovascular benefits even though they lower LDL and cholesterol (Lecerf, 2009). The effects of LA or PCB are contrary to those of n-3 omega PUFAs, disrupting the endothelial barrier function. Cellular enrichment with LA can amplify PCB induced endothelial cell dysfunction, which brings about a cardio toxic effect (Slim et al. 2001). These findings underline the importance of n-3 omega PUFAs supplementation in daily nutrition in the prevention of diseases associated with high cholesterol levels.

There appears to be significant evidence that n-3 omega PUFAs have a protective effect on the cardiovascular system and evidence of an inhibitory effect on inflammation. This evidence made n-3 omega rich foods, especially fish meat, as the most popular meat option when compared with other meats. Among red meat options, beef cut (round) may be advised with a higher α-LN content (32 mg 100/g) (as the indicator of n-3 omega PUFAs) and lower palmitic acid content (958 mg/100 g) followed by beef cut (leg) with 22 mg/100 g α-LN content and 2804 mg/100 g palmitic acid content and dark chicken meat with 25 mg/100 mg α-LN content and 1097 mg/100 g palmitic acid content (Almeida et al. 2006). Linseed oil with 55% LN content may be considered as the optimum plant oil being the richest among others although it is often neglected by the media.

It is possible that the cardioprotective effect of n-3 omega PUFAs is dependent on the anti-inflammatory properties. The anti-inflammatory properties are due to the incorporation of EPA and DHA into cell membranes. NADPH oxidase, the main producer of cell membranes,

is also activated by n-3 omega PUFAs. Only after this activation, does the enzyme regulate the cell membrane production and make it more durable and cells become more resistant to extrinsic and intrinsic destructive factors, especially inflammatory agents. This protection against inflammation is of course the same for the cells of blood vessels and the heart (Heine et al. 1999). On the other hand, when omega 3 fatty acids are provided, there is partial replacement of AA in cell membranes by EPA as one of the important members of n-3 omega PUFAs which results in strengthening of the cell (Calder, 2003a,b).

The anti-inflammatory and cardioprotective functions of n-3 omega PUFAs improve the immune system. This improvement which is very important for immune system diseases such as HIV/AIDS, requires nutrients to power the immune system and support maximum cellular protection and function for long term survival. It can be clearly stated that, n-3 omega PUFAs have potential as an immune system defenders and enhancers in immune system deficiencies (Zimmerman, 1997).

n-3 omega PUFAs and diabetes

Diabetes, remarkably increases plasma glucose, fructosamine, triglyceride, LDL and decreases HDL. It also enhances oxidative susceptibility of LDL, catalase activity and NO (nitrous oxide) levels, while increasing the synthesis and release of cytokines (IL-1 and TNF). During the treatment of diabetic rats with n-3 omega PUFAs, a significant decrease of LDL with plasma triglyceride and cytokine synthesis was noted (El-seweidy et al. 2002). One of the very few studies related to the serum glycogen level and n-3 omega intake detected lower glycogen concentrations in n-3 omega fed rats, when compared with casein fed rats (Gavia *et al.*, 2003). The studies of El-seweidy et al. (2002) and Gavia et al. (2003) seem to support the proposal that PUFAs may have a role in the treatment of diabetes because of their availability to lower blood sugar levels and reduce the hazards associated with inflammation. More studies are needed to highlight the sugar lowering effect of n-3 omega PUFAs in human serum profile.

n-3 omega PUFAs are also used for the treatment of diseases in gastrointestinal origin and especially the stimulation of PGE1 secretion by n-3 omega PUFAs by decreasing platelet aggregation (Levy and Herzberg, 1996).

The effect of treatment with n-3 omega PUFAs is closely related to the form of the fatty acid used. Pure EPA supplementation in the ethyl ester form always has a greater effect than fish oil because of the easier absorption of the ethyl ester through the intestinal wall without requiring lipase. As an example, platelet reactivity is more inhibited by pure EPA dietary supplementation than it is, when supplementation is with fish oil extract (Wojenski et al. 1991).

PUFAs, brain health and neurological disorders: Phospholipids make up 60% of the dry weight of the brain. An increase in phospholipid concentration of brain cell membranes has a significantly beneficial effect on the treatment of schizophrenia (Horrobin et al. 2002). New pharmacological mechanisms for the treatment of schizophrenia have included omega 3 fatty acids as well as partial dopamine D2-receptor

agonism, glutamatergic agents and oestrogen (Fleischhacker, 2003). Phospholipids are also essential for neurone function, especially for synaptic structure and play a key role in the signal transduction responses to dopamine, serotonin, glutamate and acetyl choline. n-3 Omega PUFAs, by controlling the over-activity of T-cells and antiphospholipid antibodies may be effective in decreasing the severity of major depression events (Maes et al. 1993). The same relationship between low numbers of major depression incidents and high levels of omega 3 supplementation has been reviewed by Colin et al. (2003). On the other hand, these inflammatory processes mentioned above, may influence the levels of neurotransmitters, especially by decreasing serotonin levels. n-3 Omega PUFAs, by enhancing the production rate of serotonin, can also reduce the severity of depression (Maes et al. 2007; Song et al. 1998). In cases of depression, there are abnormally low levels of omega 3 PUFAs and EPA whilst excessive amounts of omega 6 PUFAs are seen. The unsaturated fatty acid components of phospholipids are abnormally low in depression, with deficits of eicosapentaenoic acid and other n-3 omega PUFAs and excesses of the n-6 omega PUFA (AA). Despite this, n-3 omega PUFAs can not be administered to the patients as an effective monothreapy to treat depression. However, adjuvant application of folic acid, *S*-adenosyl-methionine, n-3 omega PUFAs and L-tryptophan with antidepressants may be beneficial, particularly in people with both depression and dietary deficiency (Sarris, 2009). Hamazaki et al. (2005) examined the effect of n-3 omega PUFAs on catecholamines (adrenaline and noradrenaline). In a randomised, placebo controlled double blind study, daily doses of 762 mg EPA + DHA lowered the noradrenaline concentration in blood. Noradrenaline is an important catecholamine which closes vessels and increases blood pressure in many cases of stress and depression. This randomised, placebo controlled, double blind study is the only study, presently, as related to n-3 omega PUFAs and catecholamines. Hallahan et al. (2007) found significantly greater improvements in depression, suicidality and daily stresses by 1.2 g EPA or 0.9 g DHA supplementation as combined with psychiatric care for 12 weeks. Laure and Marc (2006) observed a progressive decline in anxiety as compared with placebo in patients who were given 3 g of EPA and DHA for 3 months as compared with patients

receiving a placebo. Similarly, Yehuda et al. (2005) observed reduction of high cortisol levels back to normal values and remediation of sleep disturbances and anxiety during 'test anxiety' (an anxiety which may be defined as incapacitating academic syndrome) in students supplied with 225 mg n-3 and n-6 omega PUFAs. Nemets et al. (2006) claimed highly significant therapeutic effects of 1 g/day supplementation of n-3 omega PUFAs for 16 weeks in children with childhood depression, between the ages of 6–12 years. Similarly, the same dose, 1 g EPA supplementation in twenty-four patients with depression, was claimed as beneficially effective in another double blind, randomised, placebo-controlled study (Frangou et al. 2006). According to a meta-analysis among randomised controlled trials by Freeman et al. (2006), although there is less evidence of benefit in schizophrenia, EPA and DHA may have some potential benefit in major and bipolar depressive disorder but the authors conclude that results remain inconclusive (Freeman et al. 2006).

Frasure-Smith et al. (2004) examined the relationship between depression and omega 3 and 6 serum levels in patients at the age of 54 years and older in the recovery period from acute coronary syndromes in a case control study. Depressed patients had significantly lower concentrations of total n-3 omega PUFAs and higher ratios of AA to DHA and AA to EPA. They also concluded that their study was a case control study and should have been supplied by both prospective studies and randomised trials.

Antalis et al. (2006) point out that lower levels of long-chain PUFAs, particularly n-3 omega PUFAs in blood have repeatedly been associated with a variety of behavioural disorders including attention-deficit/hyperactivity disorder (ADHD). They reported in their meta-analysis that one small randomised controlled trial with n-3 omega PUFA supplementation in depression in children found a small beneficial effect over placebo. Four placebo controlled trials showed uncertain benefits of n-3 omega PUFAs for children with ADHD while a single placebo controlled trials showed no benefit in autism or bipolar disorder. Reviewers also concluded an absence of studies examining the benefits for first-episode psychosis or schizophrenia in children and adolescents (Clayton et al. 2007). A very high dose, 10 g $day^{-1}$of EPA was claimed to ameliorate the symptoms of schizophrenia while AA

had no similar effect (Peet et al. 1997). Unfortunately, this study was a small scale study so that two out of the five patients had been taken out of the study due to clinical deterioration. In one of very few studies related to the association of n-3 omega PUFAs and schizophrenia, Fenton et al. (2001)administered 3 g/d of EPA for 16 week in their double blind, controlled trials, involving eighty-seven patients, but found no difference in improvement in symptoms of schizophrenia and cognitive impairment. Joy et al. (2006) reviewed research findings related to the effects of PUFAs for people with schizophrenia between 1998 and 2002. Limited evidence supports a hypothesis suggesting that schizophrenic symptoms may be the result of altered neuronal membrane and metabolism and neuronal membrane structure and metabolism which are closely dependent on blood plasma levels of n-3 omega PUFAs and their metabolites. The authors of the meta-analysis indicate to the necessity of further large well designed, conducted and reported studies since the results in the field remain inconclusive with very little useful data.

According to Hibbeln (1998), the prevalence of depression is inversely related to the amount of fish consumed. Similarly, other groups have reported a decrease in the ratio of n-3 omega fatty acids to n-6 omega fatty acids in the plasma and erythrocytes of patients with major depression and a decreased n-3 omega fatty acid concentration in erythrocytes with an increased severity of depression (Edwards et al. 1998; Peet et al. 1998). Also, a lower DHA content in mothers milk and lower seafood consumption are associated with higher rates of postpartum depression while omega 3 PUFAs supplementation of the mothers diet improves psychomotor development, cognitive development and birth weight without the risk of negative nitrogen balance which is always caused by n-6 omega PUFAs (Morley, 1998; Hayashi et al. 1999; Woltil et al. 1999; Hibbeln, 2002). Unlike n-3 omega PUFAs, which decrease cytokine production and depression, n-6 omega PUFAs increase cytokine production and therefore, may also directly stimulate depression. However, indirect effects such as the metabolic disorders including cardiovascular diseases, immunological activation, cancer, diabetic complications and osteoporosis may lead to depression or be associated with depression. By protecting against

cardiovascular diseases, inflammation, cancer and diabetes, n-3 omega supplementation appears to have the function of reducing the risk and severity of depression both directly and by alleviation of these disorders (Horrobin, 2001). Also, Dyall and Michael-Titus (2008) indicates that increased intake of long chain n-3 omega PUFAs, EPA and DHA may confer benefits in a variety of psychiatric and neurological disorders in neurodegenerative conditions, although the mechanisms underlying these beneficial effects are still poorly understood.

Finally, in the case of AD, various genetic, medical and environmental factors appear to be causative. The risk of AD increases, when one of these factors leads to a decreased cerebral perfusion, which causes an insufficient flow of blood to the brain. Thus, the beneficial effects of n-3 omega PUFAs can decrease the risk of AD by easing the flow of blood in the brain and central nervous system (Heininger, 2000).

n-3 Omega PUFAs and eye health: One of the fields which needs further investigation and evidence as related to the effects of n-3 omega PUFAs is on eye health. One disease of the eye which has been most studied is age related macular degeneration (ARMD), an illness that progressively degenerates the back of the eye (macula). There is also insufficient evidence with few prospective studies and no randomised clinical trials to support n-3 omega PUFAs routine consumption for ARMD prevention (Chong et al. 2008). However, Chiu et al. (2009) claim in their study that weekly consumption of two or three portions of fatty fish can be beneficial for ARMD patients. The claim is based on an 8-year study of 3000 patients who were given n-3 omega supplements and monitored for the possible development of macular degeneration. Findings determined ARMD 25% less likely among participants consuming a diet rich in omega 3 fatty acids, EPA and DHA. The authors concluded that the combined consumption of a diet rich in omega 3 with low glycemic index carbohydrates such as whole bread products rather than processed may diminish the risk of progression of the disease to the advanced state. Deficiency of n-3 omega PUFAs was also shown to be adversely effective especially on visual and neural function in preterm infants which may need to be supported by n-3 omega formulas since n-3 omega PUFAs rich formula supports for visual and cortical function significantly in such infants (Hoffman et al. 1993).

Causes of ARMD have still not been identified although any arterial plaque may also affect the delicate blood vessels in the eye. Because of such possibility, it is commonly believed that a low-fat diet, but rich in n-3 omega PUFAs could help to guard against ARMD. In one of the studies, testing this theory, 90 000 participants over the age of 50 years, were monitored over a 12-year period. Findings of the research claimed that high intakes of LA (n-6 omega PUFA), exist in beef, pork and lamb and high amounts and trans fat in margarine appeared to increase the risk of ARMD, while the participants who consumed n-3 omega PUFAs rich foods such as tuna were about 35% less likely to develop ARMD (Cho et al. 2001). Ouchi et al. (2002) evaluated the relationship between fatty acids and ARMD by comparing the fatty acid fractions within the red blood cell membrane and plasma of 11 ARMD patients and ten healthy individuals (controls). They determined that there was a higher AA and DHA in the controls than in the ARMD patients which indicates that PUFAs, vulnerable to free radicals and reactive oxygen species, easily peroxidised, may be related to ARMD induction. Another study that claims the beneficial effects of n-3 omega PUFAs on eye health was conducted by Seddon et al. (2001). In the case study with 349 individuals at the age of 55–80 years, a higher intake of vegetable, monounsaturated and polyunsaturated fats and linoleic acid (n-6 omega PUFA) in 8 years was claimed to be associated with a greater risk for advanced ARMD while diets high in n-3 omega PUFAs and fish were inversely associated with risk for ARMD when intake of LA was low. Opposite to the findings of mentioned studies which indicates to the beneficial effects of n-3 omega PUFAs on ARMD, any significant relationship between age-related maculopathy and dietary fat including n-3 omega was not detected in a large cross-sectional survey of 7883 participants aged between 40 to 79 (Heuberger et al. 2001). Confirming this, oral n-3 omega PUFA supplementation as 1000 mg/d did not make any effect on improving visual activity recovery time. The authors underlined the importance of combined use of n-3 omega PUFAs with photodynamic therapy for ARMD in order to improve retinal metabolic function only under this combined use up to an extent (Scorolli et al. 2002). Since n-3 omega PUFAs exert important effects on eicosanoid metabolism, membrane properties and gene expression, it is

reasonable to hypothesise that maternal n-3 fatty acid intakes might have significant effects on infant visual function and neurodevelopmental status. There is also very limited data as related to the effects of n-3 omega rich nutrition and supplementation during postpartum period on visual acuity of infants. In one of these studies, 1.3 g n-3 omega PUFAs supplementation of lactating women for the first 4 months of postpartum also did not effect visual acuity of infants (Lauritzen et al. 2004). Similarly, DHA in algae origin, but with a lower dose (200 mg/d), was given to lactating women during the first 4 months of postpartum. It had no effect on either neurodevelopmental progress of the infants at 12 months of age 4 years or the visual function at 4 or 8 months of age (Jensen et al. 2005). Confirming these earlier findings, Gibson et al.(1997) claimed that, 200, 90 and 130 mg/d DHA supplementation of breast feeding women during the first 12 week of postpartum period did not effect visual acuity of the infants. No clear consensus exists in studies as related to the effects of n-3 omega PUFAs on infant visual function and neurodevelopmental status of infants while only a few available data suggest a modest effect (Jensen, 2006).

Findings clearly indicate that a definite effect of n-3 omega PUFAs on eye health can not be claimed because some of the findings, especially those based on findings of meta-analysis are conflicted while some of the researches needs further evidence of more prospective studies and randomised clinical trials in 'n-3 omega and eye health relation'.

Questions still waiting to be highlighted: In addition to their reputed beneficial effects supported by strong scientific evidence (Davidson and Geohas, 2003), omega 3 PUFAs have one notable adverse side effect, they stimulate oxidation (Nardini et al. 1995) which necessitates the regular use of an antioxidant, commonly Vitamin E (Arkhipenko and Sazontova, 1995; Linseisen et al. 2000; Gil, 2002) in combination with n-3 omega PUFAs. Using such an antioxidant, can easily lower the excessive oxidation rate, induced by these fatty acids (Puiggros et al. 2002). The conjoint use of n-3 omega PUFAs and vitamin E (α-tocopherol) after surgery in the stomach, intestines and digestive organs, protects patients against inflammation in the postoperative period, without increasing lipid peroxidation (Linseisen et al. 2000).

Despite the substantial amount of knowledge related to the

anti-inflammatory and sleep promoting effects of n-3 omega PUFAs, the minimum effective doses have not been sufficiently determined. Establishing such correct doses will require a considerable amount of time and research, due to the spontaneous metabolic conversion of omega 3 and omega 6 fatty acid into each other and the differences in each persons unique serum omega profiles.

The potential of PUFAs to increase energy utilisation has not yet been clearly demonstrated due to a lack of studies related to their use as energisers in sports and postoperative periods (Emmanuel and Hubbard, 1993). Oxygen free radicals (OFR) are very effective in the development of hypercholesterolemic atherosclerosis, resulting due to excessive cholesterol on the inner layer of blood vessels. IL-1, LTB4 and TNF are the end products of PGE2 metabolism which stimulate polymorphonuclear leucocytes and monocytes to produce OFR. The n-3 omega PUFAs reduce the rate of production of OFR by inhibiting the production of IL-1, LTB4 and TNF (Prasad, 1997). However, they are also highly susceptible to the oxidation themselves. Thus, the long-term treatment at a high dose (7.7 g/d) with these fatty acids also causes an increase in lipid peroxidation. Therefore, the risk of this oxidation on plasmic membranes of red blood cells should be considered as a serious side effect in nutrition with n-3 omega PUFAs (Bartoli et al. 1995). Similarly, incorporation of long-chain n-3 omega PUFAs in LDL, results in a decrease in its resistance of LDL to oxidation because of the high degree of unsaturation of these fatty acids. A study conducted on rats, indicated a decrease in plasma antioxidant potential and an increase in the susceptibility of LDL to oxidation (Nardini, 1995). In contrast, Brude et al. (1997) found no difference in LDL particle susceptibility to oxidation between a group receiving n-3 omega supplement and a group receiving a placebo.

Another major problem when employing n-3 omega PUFAs in the food industry is the risk of oxidation in meat products enriched with n-3 omega PUFAs. O'Keefe et al. (1995) showed that, in meat of poultry which were fed with 8% and 12% fishmeal, high levels of peroxide developed during refrigeration. Similarly, supplementation of the diet with fish oil (as n-3 omega source) was not effective on colour retention and oxidative stability of lamb during refrigeration,

according to Ponnampalam et al. (2001). These results seem to be far from highlighting oxidative stress due to n-3 omega supplementation of the foods but what we definitely know is the necessity to use n-3 omega PUFAs as combined with fat soluble antioxidants, not only in human metabolism but also in meat and meat products. These results have shown that the PUFAs should be combined with antioxidants to achieve their protective effects. Given the apparent importance of these PUFAs to human health, it is hoped that meat producers and meat scientists will develop methods for including omega 3 in meat, meat products and animal feed possibly via feeding regimes including appropriate antioxidant support. Otherwise, omega 3 use in meat industry without antioxidant addition may result in oxidation and discolouration of meat rather than an increase in meat quality.

Contrary to preconceived opinions, EPA and DHA (as the precursors of n-3 Omega PUFAs) have no significant relevance in the evaluation of the omega quality of fish and marine products, since AA and EPA, DHA, LN can be converted into each other. Therefore, when evaluating the nutritional quality of foods, the ratio of total fat content to the amount of EPA and DHA should be considered rather than the content of DHA and EPA, separately. This ratio should be as small as possible, as in halibut, cod, haddock and tuna. α-LN andAA do not mean anything by themselves, since they can be readily converted into each other. The ratio of total fat content to the total amount of α-LN may also be considered as the main criterion in determining the omega quality of oils.

Areas of future research: Whilst the beneficial effects of n-3 omega PUFAs on metabolism such as reducing the risk of cancer, cardiovascular diseases (esp. atherosclerosis), many inflammatory disorders (such as ulcerative colitis, Crohn's disease and asthma), diabetes, depression and even AD have been indicated, the effective doses for each of these diseases and individual patient requirements still wait to be determined.

Although we have got important scientific evidence and data as related to the protective effects of n-3 omega PUFAs in cardiovascular health and cancer, we still do not know the mechanism of these effects. Further studies are needed to investigate these mechanisms.

Another important question which is requiring investigation appears

as the antagonism of dietary fibre and omega 3 fatty acids in some omega 3 rich food products. Flax seed, purple grape seed, canola seed with many others, are used by many people as omega 3 supplements in many countries. But, 'should we trust to the omega 3 contents of these food supplements since they also contain high amounts of dietary fibre, such as lignan, which can bind some omega 3 fatty acids and decreases their bioavailability?' is another question to be highlighted. Studies are needed to determine which fibres bind which omega 3 PUFA and the relevance of these interactions in each product or food material. Otherwise, many people in the world will continue to use omega 3 from these types of supplements despite the fact that, these fatty acids are bound to the fibre and therefore excreted directly without being absorbed by body and hence without effect.

Some studies used to administer very high doses of n-3 omega PUFAs, like 10 g/d and 6.6 g/ d administrations by Peet et al. (1997) and Su et al. (2003). Both studies claimed beneficial effects of these megadoses on depression and schizophrenia. However the risk about internal bleeding risk due to the anticlotting effect of n-3 omega needs to be considered when administering large megadoses. The findings will no more be important, no matter how they claim beneficial effects, as long as the risk of internal bleeding in the administration of megadoses is always possible. This important point should always be taken into consideration in further studies.

Suzuki *et al.* (2004) examined the association between daily intake of n-3 omega PUFAs and depression in Japanese cancer patients. In this big scale study (with 771 patients), their findings indicated that there was no association between EPA and DHA intake. The research raises a question which needs further studies to be highlighted, 'which one has got stronger association with cancer; α-LN intake or EPA and DHA intake?'. Confirmatory studies are needed.

Another question with omega 3 seems to be the reliability and the sensitivity of some of the mentioned and other research as related to omega 3. In many instances, the authors indicate the necessity to use conditional statements rather than definite expressions when discussing and evaluating n-3 omega studies. For example, how can we trust definitely and completely to the use of terms such as 'Western style'

or 'Far East style' nutrition when there may be a significant dietary personal variations which use lower or higher amounts of n-3 omega. In other words, variations in exposure at the population level do not always correspond to variations among individuals within any given population. Therefore, we should note that, we need case controlled studies rather than cohort studies or cohort-controlled studies that should compare individuals with high and low consumption within populations. Also, like western style and east style nutrition, term 'fish oil' seems insufficiently specific and clear since EPA and DHA (n-3 omega in fish oil) vary between fish species although high concentrations are found in cold water species such as salmon, mackerel, herring and sardines, whilst only low concentrations are found in lean fish such as sole, cod and halibut. Similarly, whiting deposits most of its n-3 omega content into its abdominal cavity and naturally loses this content during evisceration prior to cooking. Therefore, in order to conduct an accurate evaluation of the effects, we need to know fish species, fish oil type and the person, with his/her exact daily nutrition profile. In the evaluation and consideration of new future studies as related to n-3 omega fatty acids and their beneficial effects, rather than general terms such as African or western style or fish oil, the mentioned approach may increase the sensitivity and reliability of the research on n-3 omega. Otherwise, there will still be conflicting reports or studies with poor sensitivity and there will have to use of possibility terms rather than definite expressions about the beneficial effects of dietary supplementation with n-3 omega fatty acids.

What is the situation in relation to the side effects of n-3 omega PUFAs such as fattening of mucosa, the risk of internal bleeding or their unfavourable interaction with other food ingredients? Despite the lack of knowledge in relation to adverse effects, omega 3 supplements are still being used without control in an attempt to decrease the mortality rate associated with certain diseases. Clinically, this often leads to serious side effects such as bleeding from an excessive intake of n-3 omega or thrombosis and emboli from an excessive intake of n-6 omega fatty acids.

Conversely, the studies of O'Keefe et al. (1995) and Ponnampalam et al. (2001) showed either high peroxide or no change in peroxide

respectively, following omega 3 supplemented feeding of poultry and mutton which conflict with other studies showing the antioxidant effects of omega 3 fatty acids. Thus, it is unclear whether n-3 omega PUFAs are oxidants increasing peroxide in meat products or antioxidants.

Promising n-3 Omega PUFA supplies for future

The primary sources of n-3 omega, are some algae and fungi from the order Mucorales (Bajpai and Bajpai, 1993), Ooligan grease (*Thaleichthys pacifus*) (Kuhnlein et al. 1996), Camelina sativa L. Crantz seed (Rokka et al. 2002) and sea/fresh water fish, vegetable and oil products (Sauci et al. 1994). Recently, interesting and promising studies have succeeded in extracting high EPA levels from diatoms such as *Phaeodactylum tricornutum* which seems less expensive than from cod liver (Lebeau and Robert, 2003). Similarly, DHA-rich oil content from microalgae, Ulkenia sp., improved some CHD risk factors, resulting in lower TG:HDL cholesterol and plasma TG but increased LDL cholesterol (Geppert, 2006). Unfortunately, these studies are also very few with a very limited scientific evidence and data.

Future research required

When all the above-mentioned studies which were also analysed and referred in the review of Gogus and Smith (2010) are considered, it is possible to say that n-3 omega PUFAs are clearly beneficial food supplements, especially with their protective effect on cardiovascular system. Most of the patients, who are receiving treatment in cardiology and neurology clinics in the USA, are given an anticoagulant, in combination with a weekly diet programme. The dietary program is used to counteract the dosing inadequacies related to the anticoagulant. Thus, the prothrombin (Ptz) time (a criteria for determining the clotting level of blood) is monitored and when there is an excessive anti-clotting due to an overdose of the anticoagulant, the diet is changed to one, low in omega 3 whilst, in cases of anticoagulant insufficiency which results in high levels of coagulation in the blood as confirmed by a short Ptz time, the diet is changed to one, rich in omega 3. Unfortunately, this approach is not being adopted in the hospitals of most European, Middle East, Asia and Far Eastern countries. Research supporting this treatment is needed to encourage its more extensive use.

According to FAO/WHO, the recommended dose of essential PUFAs in a healthy diet in daily nutrition is 5–10:1 (n-6:n-3) (Trautwein, 2001), but this dose was not established on the basis of different serum DHA and EPA levels and the effect of the dose on these levels. Interestingly, 5–10:1 (n-6:n-3) intakes, recommended by FAO/WHO have been proven to have adverse effects on metabolism (Simopoulos, 2002b). Further, there is no study about serious side effects (such as internal bleeding) that arise from an excessive intake of n-3 omega PUFAs. Thus, more information relating to the appropriate intake levels is needed.

Although there is no doubt of their beneficial effects, indeed, they might even be considered an essential to be one of the basic nutritional components of daily nutrition. However, their efficacy is dependent upon the ratio of n-6:n-3 and the condition being treated. It has been established that, only lower ratios between 2.5:1(n-6:n-3) and 5:1(n-6:n-3) are beneficial while a daily intake of 2.5:1(n-6:n-3) has been proven to act

beneficially in cases of colorectal cancer, 2–3:1(n-6:n-3) on rheumatoid arthritis, and 5:1(n-6:n-3) on asthma (Simopoulos, 2008). Interestingly, 5–10:1 (n-6:n-3) intakes, recommended by FAO/WHO, have been proven to have adverse effects on metabolism (Simopoulos, 2002b). The recommended average daily n-3 omega PUFA intake was recommended to be increased from 0.1 to 0.2 g/d by the UK dietary guidelines while it was recommended as above 0.2 g/d by Committee on Medical Aspects of Food Policy (COMA) that the current UK recommendation for the intake of n-3 omega PUFAs seem to need to be revisited (Ruxton et al. 2007). American Heart Association (Lichtenstein et al. 2006) and The American Dietetic Associations of Canada (Kris-Etherton and Innis, 2007) recommend daily intakes of EPA and DHA as 0.5–1.0 g. Institutes of Medicine recommends as 0.11–0.16 g and The American Dietetic Associations of Canada (Kris-Etherton and Innis, 2007) recommends the same amount with American Heart Association as 0.5 g. Additionally, the recommended daily intakes, in cancer, diabetes, ulcerative colitis, Crohn's disease, asthma, depression and AD, have yet to be determined and thus represent an important area for future study. Thus, studies to define the recommended dose are still needed.

Catecholamines (adrenaline and noradrenaline) play an important role in stress and depression by constricting and dilating blood vessels. We have got no data, except only Hamazaki et al.(2005) who have mentioned the importance of PUFAs in relation to brain health and neurological disorders. So, the association between n-3 omega PUFAs and catecholamine metabolism needs further studies to be highlighted. Also, in spite of a limited data and evidence about the association between n-3 omega PUFAs and schizophrenia and, the potential effects of the fatty acids in schizophrenia remains completely unclear with many questions waiting to be answered.

One of the missing field about n-3 omega PUFAs which should be studied, is the effect on quality of pregnancy although a randomised, double-blind, placebo controlled study in UK in 113 high risk pregnancy showed no evidence for any useful effect of 1.62 g EPA and 1.08 g DHA supplementation for women at high risk of adverse outcomes from pregnancy during 38 weeks of gestation (Onwude *et al.*, 1995). Rump et al. (2001) examined the relation between cord plasma essential fatty acid

composition and birth weight and indicated a positive relation of dihomo α-LN concentration to birth weight scores in spite of a negative relation of both AA and DHA. In spite of the association between dihomo α-LN concentration and birth weight, there is not any study yet, to highlight the effects of n-3 omega rich consumption during pregnancy on birth weight.

Allograft coronary arteriosclerosis, hardening of the arteries followed by organ transplantation is a common problem in cardiology. Sarris et al. (1989) administered 3 mg/kg/d fish oil to rats for 11 days, followed by heart allograft. Their findings demonstrated that fish oil supplementation inhibited accelerated coronary arteriosclerosis in heart allograft immunosuppression. But, the material in the study is animal. Additionally, 3 mg/kg/d, dose is a mega dose which may cause side effects such as an increased risk of internal bleeding in the case of their long-term use. Also, the long-term use of them without an antioxidant can trigger oxidation and free toxic peroxy radical production. The use of lower doses as combined with an appropriate antioxidant to ameliorate allograft coronary arteriosclerosis in man should be investigated with further studies.

The very limited number of studies as related to the new n-3 omega sources such as algae and the effects of n-3 Omega PUFAs, DHA and EPA, in microalgae origin, requires further investigation. Such biotechnology studies are urgently needed to create diets rich in n-3 omega by using rich omega 3 fatty acid contents of these types of micro-organisms.

Unfortunately, there seems to be no study related to the effects of n-3 omega intake on bone and skeletal health. Only one study, on rats, carried out by Sirois et al. (2003), showed that feeding fish oil to males had no effect on the biochemical strength of femurs and vertebrae as measured by three point bending and compression whilst females fed the same fish oil diet had reduced growth in length and a lower vertebral peak load. More investigation is required to highlight the effects of n-3 omega PUFAs on human bone strength and susceptibility to fractures.

In spite of some available data and evidence about association between n-3 omega PUFAs and depression, anxiety and schizophrenia, we have got very few data as related to the association between n-3

omega PUFAs and dementia. According to the findings of Cherubini et al. (2007), people with dementia have significantly lower levels of n-3 omega PUFAs in their blood than people at the same age with normal cognitive function while there was no relation between dietary intake of n-3 and n-6 omega and dementia in the study of Devore et al. (2009). More future studies are required to highlight the association between dementia and n-3 omega PUFAs. However, most of the limited evidence and data about the relationship between of n-3 omega PUFAs and dementia claims no association between them. Kröger *et al.* (2009) evaluated the association of erythrocyte membranes, total n-3 omega PUFAs; EPA and DHA and blood mercury with the incidence of dementia and AD. The study involved 514 patients with dementia at the age of 65 and older between 1991 and 2002, but no associations between n-3 omega PUFAs and dementia or AD were found. In another study about the association of n-3 omega PUFAs with dementia, 5395 participants at the age of 55 years and older, were investigated. But, similarly, the findings did not indicate to any association of typical fish intake in high amounts for 9.6 years with dementia or AD.

A possible explanation for these negative results relates to the ease of oxidation of PUFAs. ApoE4 (Apolipoprotein E4) is a protein which is produced and inherited under the control of E4 gene. The protein attaches itself to a particular receptor on the surface of brain cells. The receptor adheres to the protein which is called as amyloid precursor protein. The brain cells transport this protein mass inside and it is attacked by proteases in the cell. The fragments which are produced by the attack are believed to cause the cell death in brain tissue. In their review, Cole et al. (2009) indicate that, high oxidative stress due to the higher concentrations of ApoE4 in very late stages of dementia and AD, limits the efficacy of n-3 omega PUFAs on dementia and AD. Another limitation is because dementia risk doubles with every 5 years over age 65 years. Therefore, the initial protective effect of the fatty acids against dementia and AD may be due to their protective effects against cardiovascular diseases rather than their direct effect. Cole et al. (2009) included that a direct association of n-3 omega PUFAs with dementia and AD can not be claimed definitely, since most of the studies

are case control, small scale experiments but not randomised and large big scale studies.

It has been proposed that, the meat industry should enrich their meat products with these fatty acids. The enrichment is achieved by feeding animals with appropriate diets enriched with n-3 omega PUFAs. In one of these studies, linseed oil, forages (rich in LN) and fish meal were used as the feed ingredients for beef, mutton and pork, prior to the slaughter (Raes et al. 2003). However, there have been no studies on serum cholesterol and n-3 omega levels of meats followed by consumption of these n-3 omega enriched diets in the period before slaughter. After such studies have been carried out, n-3 omega PUFAs might become the basic anticholesterolemic additives of the meat industry.

It has been suggested by Levy and Herzberg (1996) that omega 3 supplementation inhibits platelet aggregation and therefore the same supplementation may ease bile flow and therefore assist in the treatment of renal failure. n-3 Omega may be used as a dietary measure like statins, L-carnitin and bicarbonate in the treatment of patients with chronic haemodialysis because of their LDL lowering potential (Kovacic et al. 2003). Further research is required in the field of nephrology to confirm these findings.

When it comes to the association of n-3 Omega fatty acids and Cancer

Like cardiovascular diseases, one initial predisposing factor for cancer appears to be the fat composition of the diet. Whereas an increased ratio of saturated fatty acids in the diet leads to cancer, many researchers have determined the protective effect of dietary eicosanopentaenoic acid in diet against cancer in gastrointestinal origin. Increased concentrations of long chain fatty acids and eicosanopentaenoic acid (as the main constituents of n-3 omega PUFAs) protect against colorectal cancer (Nkondjock et al. 2003). Dietary supplementation with n-3 omega PUFAs has been shown to produce beneficial effects in patients with pancreatic cancer, by decreasing tumour formation (Gogos et al. 1998) and reducing weight-loss (Barber et al. 1999). Fish oil alone or soy bean and fish oil combined dietary supplementations produced an increase in body weight in a study on rats, indicating their potential for weight gain in cancer (Gavia et al. 2003). n-3 Omega fatty acid supplementation is very effective, not only as an antitumour agent but also in mediating the effects of nutritional interventions by prolonging life span, suppressing autoimmune diseases, decreasing tumourigenesis (Troyer and Fernandes, 1996) and tumour necrosis factor (TNF; a protein which is detected in high concentrations in various types of cancer which increases T suppressor cells) (Simopoulos et al. 1991).

Unlike the significant protective and suppressing effects of n-3 omega PUFAs in cancer and autoimmune diseases, n-6 omega PUFAs increase the risk of tumour promotion, indicating the advantages of olive and canola oils, which are low in n-6 omega (Wood et al. 1996). A 3 g daily supplement of flaxseed, which is a rich source of lignan and n-3 omega PUFAs, when combined with dietary fat restriction, results in decreased prostate specific antigen levels and proliferation rate in prostate cancer (Demark-Wahnefried et al. 2001). According to Moyad (2003), one of the initial causes of death in prostate cancer patients is cardiovascular disease rather than cancer. Thus, these patients with prostate cancer should increase their consumption of omega 3 fatty

acids as well as maintaining a healthy weight and getting physical activity. The data relating to the protective effect of n-3 omega PUFAs against cancer is mainly determined by the following factors: the type of the cancer, metabolism, genes, sex, age and diet. Whereas n-3 omega PUFAs show their protective effect against cancer on metabolism by acting on the metabolism, high dietary LA (e.g. n-6 omega PUFAs) intake can elevate oestrogen levels in pregnancy, altering mammary gland morphology and expression of fat-and/or oestrogen-regulated genes and increasing breast cancer risk (Clarke et al. 1999). Theodoratou et al.(2007) found a significantly important association between n-3 omega PUFAs and colorectal cancer in a large scale meta-analysis, involving data from 1455 patients studied between 1999 and 2006 that, n-3 omega PUFAs decreased the risk of colorectal cancer whilst saturated fatty acids, namely palmitic, stearic and oleic acid increased the risk. Similarly, supplementing the diet of tumour-bearing mice with n-3 omega PUFAs was claimed to slow the growth of cancers including lung, colon, mammary and prostate, according to Hardman (2004). The author also indicates the importance of n-3 omega PUFAs as a complementary medicine which can improve the efficacy of cancer chemotherapy drugs such as doxorubicin, epirubicin, 5-fluorouracil, tamoxifen and of radiation therapy. Geelen et al. (2007), in their meta-analysis, involving fourteen studies, relating to colorectal cancer, suggested an evidence that n-3 omega PUFAs inhibited colorectal carcinogenesis but the authors also concluded that there is insufficient data available to definitively confirm this association.

According to Rose and Connolly (1999), a common feature of most of the mentioned cancer preventive activity of n-3 omega PUFAs is related to the inhibition of eicosanoid production caused by n-6 omega PUFAs. Another suggested effect mechanism of the cancer preventive effect is claimed as the inhibition of transactivation of transcription activator protein 1 (AP-1), a protein responsible from gene expressions that cause cell proliferation and tumour formation in cancer (Liu et al. 2001).

An important finding which conflicts with findings that claim n-3 omega PUFAs are significantly effective in reducing cancer risk belongs to MacLean et al. (2006). In their review, a total of thirty-eight articles

with prospective cohort study design and different levels of exposure in the cohort were included. Interestingly, in their review, a large body of literature, spanning cohorts from many countries, did not provide evidence to suggest a significant association between n-3 omega PUFAs and cancer incidence. According to this meta-analysis in the review, dietary supplementation with n-3 omega PUFAs, as conflicting with many others, is unlikely to prevent cancer.

There seems a great conflict in today's current literature about the n-3 Omega fatty acids. Some of the studies including reviews and researches define these fatty acids as antioxidant but these fatty acids are very peroxidisable and can produce Reactive Oxygen Species (ROS). The reason for the detailed information above about the beneficial effects of the fatty acids on many metabolic diseases and disorders is to be able to make an objective and sensible evaluation of the fatty acids. These fatty acids may have many beneficial and protective effects against the mentioned metabolic diseases and disorders but ROS inducing effects of these fatty acids should not be understood that they have got important risks from the point of cancer progress. As it is often mentioned in various parts, ROS have got dual effect in metabolism. The excess of ROS and a high level of oxidative stress may lead many metabolic diseases and disorders from Alzheimer, Parkinson to diabet and hypertension but the matter changes when it comes to cancer. Although ROS often appear as one of the initial predisposed factors leading to the progress of various diseases and disorders, killing tumor cells by ROS has often been a novel anticancer approach in anticancer treatments currently. The first crucial point about the fatty acids is their selective cytotoxicity towards cancer cells while these fatty acids have no toxicity or very little toxicity on normal cells. The fatty acids increase the sensitivity of tumor cells to conventional therapies. This may be due to their improving effect on treatments against to cancer cells which are resistant to such treatments (D'Eliseo and Velotti 2016). The second crucial point of the fatty acids is the killing tumor cells with their ROS and subsequently the induction of caspase depended apoptosis (Kang et al. 2010; Fukui et al. 2013).

The 'syndecans', consisting of four transmembrane heparin sulfate proteoglycans (HSPGs) which are present on the cell surface, are

involved in cell spreding, cell adhesion, cell migration, infiltration and angiogenesis(Liu et al. 1998; Beauvaris et al. 2004; Kokenyesi and Bernfield 1994; Szatmari et al. 2015). Syndecan-2 (SDC-1) has been informed to inhibit one of the anti-apoptotic signaling, MAPK/Erk/extracellular signal-regulated kinase (Erk) and Bad to induce apoptosis by damaging the phosphorylation of MAPK/Erk (Sun et al. 2011). Thus, the anticancer drugs which target tumor cells by inhibiting MAPK/ERK; varinostat, ritonavir, radicicol, tamoxifen, geldanamycin, lapatinib, fulvestrant, PD98059, UO126, honokiol and SNX212, may have a much stronger anticancerogenic effect if they are administered as combined with a a Omega 3 rich diet or supplementation, creating a synergy via the up-regulation of Syndecan-1 and as a result, inhibition of MAPK/ERK signaling.

Docosahexaenoic acid (DHA), has also been shown to inhibit another anti-apoptotic signaling, Wnt/β-catenin (Park and Kim 2017). So, Wnt and beta catenin inhibitors; sunitinib, sorafenib, SCH72965, metformin and bortezomib combination, tunicamycin, radicicol, KUSs, versipelostatin, pyrivinium pamoate, tanespimycin and 17-AAG, XAV939, IWR1, IWP-1, IWP-2, JW74, JW55, okadaic acid, tautomycin, SB239063, ADP-HPD, 2-[4-(4-fluorophenyl)piperazin-1-yl]-6-methylpyrimidin-4(3H)-one, PI34, niclosamide, cambinol, sulindac, 3289-8625, Scaffold A for series of analogs, Scaffold B for series of analogs, JO1-017a, NSC668036, Flipin, IC261, PF670462, bosutinib, PHA665752, imatinib, ICG-001, ethacrynic acid, ethacyrnic acid derivative, PKF115-584, PNU-74654, PKF118-744, C6P049090, PKF118-310, ZTM000990, BC21, GDC-0941 and Rp-8-Br-cAMP, in addition to sorafenib, RING finger protein43 (RNF43), tetrandrine, geldanamycin, FH535, fulvestrant, vorinostat, curcumin, quercetin, resveratrol, apigenin, folate, kaempferol, isohamnetin, genistein, baicalein, EGCG and sulforaphane, may benefit from a diet rich in n-3 Omega PUFAs.

The inhibitions of COX1 and 2, the antiapoptotic cyclooxygenase enzymes with their growth inducing and inflammatory effects by EPA (as more effective than DHA!), may be another anticancerogenic effect of PUFA-3 fatty acids while these fatty acids can act as the agonists of peroxisome proliferator-activated receptor-gamma (PPAR gamma)

and proinflammatory nitric oxide besides COX 1 and 2 (Groeger et al. 2010). Therefore, the anticancerogenic effects of COX inhibitors, e.g. sunitinib, celecoxib, magnolol, honokiol, eugenol, bis-eugenol, tetrandrine, 17AAG, raloxifene, rofecoxib, nafroxen, dexamethasone, hydrocortisone, triamcinolone acetonide, methyl prednisolone, beclomethasone diproprionate, may be improved if these inhibitors are administered as combined with n-3 Omega rich food consumption or supplementation.

DHA and especially EPA can induce apoptosis not only by increasing caspase activity, DNA fragmentation and the loss of mitochondrial membrane potential, but also by decreasing Akt phosphorylation as well as NFkappaBDNA binding activity (Schley et al 2005). Thus, the anticancer drugs which target cancer cells by inhibiting Akt; LY29002, SF-1126, NVP-BEZ235, XL147, XL765, ISC-4, GSK690693, MK2206, fused pyrimides, PIP3, GDC-0941, celecoxib, UCN-01, BX-795, BX-912, BX-320, CCT128930, GDC-0068, perifosine, GSK-214795, BX-320, GSK2110183, ipatasertib, afuresertib, AT13148, PF-04691502, A47867 and triciribine, may exhibit more anticancerogenic effect if they are administered as combined with Omega-3 fatty acids or supplementation. Also, the Hedgehog inhibitors; CUR-61414, HhAntag-691, GDC-0449 (in basal cell carcinoma, medulloblastoma and rhabdomyosarcoma), guggulsterone (a plant steroid, obtained from Commiphora mukul, soridegib(IPI-926) (in advanced solid tumors), phthaladines, namely LY2940680, NVP-LEQ506, itraconazole, an antifungul (in meddulloblastoma), NVP-LDE225, TAK-441, XL-139, HTS piperidines, MRT-83, PF-04449913(acute myeloid leukemia, N-acylethanolamides, 2-acylglycerols and 2-alkylglycerol (endocannabinoids), SANT1-SANT4, CUR-61414, HhAntag-691, GDC-0449, guggulsterone, saridegib, phthaladines, itracanozole, NVP-LDE225, TAK-441, XL-139, HTS piperidines, MRT-92, MRT-83, PF-04449913, N-acylethanolamides, 2-acylglycerols and 2-alkylglycerol, may have much stronger anticancerogenic effect if they are administered during a Omega 3 fat rich nutrition or supplementation, creating a synergy via the inhibition of Hedgehog signaling.

n-3 Omega fatty acids can increase reactive oxygen species (ROS) since they are highly peroxidisable and therefore, can increase ROS

which may result in apoptosis (Park et al. 2013). So, the drugs which kill cancer cells by producing ROS, namely; sunitinib, sorafenib, tetrandrine, cisplatin, bortezomib, vorinostat, MG-132, metformin, thapsigargin, tunicamycin, 17AAG, DBeQ, ritonavir and brefeldin A, may have more anticancerogenic effect if a Omega 3 rich food nutrition and/or supplementation is followed during the administration of these drugs.

The expression of p38, the mitogen activated protein kinase which has dual effect, may induce apoptosis or prevent apoptosis, depending on the stimuli and cellular context, has been informed to be inhibited by DHA (Serini et al. 2008). Therefore, the anticancer drugs which kill tumor cells by overactivating p38, namely; cisplatin, transplatin, platinum (IV) chloride, brefeldin A, thapsigargin, tunicamycin, tamoxifen, betulinic acid, honokiol, bortezomib, 4-phenyl-3-betulinic acid (PBA), vorinostat, geldanamycin, raloxifen, paclitaxel and panaxydol can be effected adversely and may lose from their anticancerogenic effects if n-3 Omega PUFAs rich food nutrition or supplementation is followed during their administrations, creating an antagonism.

DHA has also been informed to inhibit GRP78, the central regulator of endoplasmic reticulum function because of its protein folding capacity as a chaperon. DHA induces apoptosis by altering the expression and cellular location of GRP78 in colon cancer cells (Fasano et al. 2012). Thus, the anticancer drugs, namely; sunitinib, sorafenib, tetrandine, cisplatin, bortezomid, vorinostat, MG-132, metformin, thapsigargin, tunicamycin, versipelostatin, tanespimycin, HKH40A, WMC79, pyrivinium pamoate, eeyarestatin, metformin and bortezomib combination, 17AAG, DBeQ, ritonavir and brefeldin A, all of which induce apoptosis via the inhibition of the chaperon's activity, may benefit from n-3 Omega rich food nutrition and/or supplementation, creating a synergy through the inhibition of the chaperon.

n-3 Omega fatty acids induce Nrf2 (the protein which is called nuclear factor erthyroid-derived 2). Nrf2 controls phase II enzymes (e.g. CYP1A1, CYP2A2..) which increase the solubility of these toxic compounds and reduce their toxicity (Zhang et al. 2014). As previously mentioned, sulforaphane may create a smart combination, creating a synergy via the induction of the gene, Nrf2. Other words, a fish dinner

with broccoli or Brussels sprouds, may be a useful option for the patients with cancer. On the other hand, the same fatty acids induce HO-1 activation (Choi and Alam 1996).

The overall anticancerogenic and cancerogenic effects may be summarized best by Black and Rhodes (2016) via 7 mechanims. 1. Increasing levels of dietary omega-6 polyunsaturated fatty acids exacerbate UVR carcinogenic expression, with respect to both shortened tumor latent period and increased tumor multiplicity. 2. Dietary omega-3 polyunsaturated fatty acids inhibit UVR (Solar Ultraviolet Radiation) carcinogenic expression. 3. Omega-6 polyunsaturated fatty acids exert their principal effect upon the post-initiation, or promotion/ progression stages of UVR carcinogenesis. 4. Omega-3 polyunsaturated fatty acids appear to exert their principal effects during the initiation stage of the carcinogenic continuum. 5. Pro-inflammatory and immunosuppressive PGE2 (the proinflammatory, immunosuppressive and procancerogenic cytokines) levels are increased linearly as dietary omega-6 polyunsaturated fatty acid levels increase. 6. Pro-inflammatory and immunosuppressive PGE2 levels are dramatically reduced by dietary omega-3 FA intake 7. Dietary omega-6 polyunsaturated fatty acids suppress the immunologic responses involved in tumor transplant rejection and the immunologic pathways involved in DTH (Deleyed Type Hypersensitivity) and CHS (the animal model in which the immunological mechanisms of allergic contact dermatitis in humans can be studied) and 8. Dietary omega-3 FA inhibit UVR-induced suppression of DTH and CHS.

Cohorts about the association of n-3 Omega and n-6 Omega PUFAs with cancer

- The highest quartile of fish consumption from 14 different cohorts with the pooled Relative Risk (RR): (0.78, 0.58-1.06, 95% CI) for women and 0.94, 0.75-1.18, 95% CI) for men and the pooled RR for the highest quartile of fish consumption compared to the lowest (1.02,0.90-1.16, 95% CI) decreased the risk of colorectal cancer (Geelen et al. 2007).
- 827.833 person, 1268 patients with colorectal cancer, 521 colon cancer/40-71 years of age/alcohol and smoking adjusted/9.3 years of follow up/the highest quartile of n-3 Omega PUFA intake (0.60, 0.31-1.14, 95% CI) versus the lowest (0.35, 0.14-0.88, 95% CI) decreased the risk of colon cancer (Sasazuki et al. 2011).
- 498 control, 363 colorectal adenoma/18-75 years of age/alcohol and smoking adjusted/1997-2002/the highest quartile of n-6 Omega PUFAs (1.68, 1.17-2.42, 95% CI) increased the risk of colorectal adenoma whereas the highest quartile of n-3 Omega PUFAs (0.67, 0.46-0.96, 95% CI) decreased this risk (Pot et al. 2008).
- 442.965 person, 4.653 death / 55-69 years of age / alcohol adjusted, smoking adjusted / 1987-1997 / The highest quartile of n-3 Omega PUFA intake (1.01, 0.85-1.20, 95% CI) (≥2.5 g/d) versus the lowest (0.96, 0.87-1.24, 95% CI) decreased the risk of breast cancer (Folsom and Demissie 2004).
- 22.494 women, 263 endometrial cancer / 9 years of follow up / 50-76 years of age / 50-76 years of age / smoking adjusted, alcohol adjusted / >84 mg/d as the highest quartile of n-3 Omega PUFAs intake (1.73, 1.14-2.63, 95% CI) versus <18 mg/d as the lowest (R:1.00, 95% CI) decreased the risk of endometrial cancer (Brasky et al. 2014).
- 1951 control, 565 colorectal cancer / 62.2-61.1 median years of age /alcohol adjusted, smoking adjusted / the highest quartile of

n-3 Omega PUFAs (0.82, 0.59-1.13, 95% CI) versus the lowest R:1.00, 95% CI) decreased the risk of colorectal cancer (Key et al. 2012).

- (1.02, 1.00-1.05, 95% CI) as the lowest versus (0.99, 0.98-1.00, 95% CI) which represents 0.5 g/d increase in n-3 Omega PUFAs intake decreased the risk of prostate cancer / 16 published studies were analysed in 2014 (Fu et al. 2015).
- (0.15-0.76, 95% CI) as the highest quartile versus (0.47, 0.25-0.88, 95% CI) decreased the risk of Barett's esophagus / In contrast, higher red meat intakes were associated with increased risk (0.25, 0.09-0.72, 95% CI) (Kubo et al. 2009).
- N-3 Omega PUFAs during parenteral nutrition reduced inflammation and improved immune function in 60 patients following esophageal cancer surgery (Long et al. 2013).
- 943 control, 929 distal large bowel cancer / 40-79 years of age / 2002-2006 / smoking adjusted, alcohol not / (0.88, 0.63-1.22, 95% CI) versus (0.49, 0.34-0.71, 95% CI) as the highest quartile decreased the risk of distal large bowel cancer where as n-3 Omega 6 increased the risk (Kim et al. 2010).

Presently, there is an important amount of scientific data as related to the beneficial and protective effects of n-3 omega PUFAs and their effects against inflammation, cancer and heart diseases. The association between major and bipolar depression, schizophrenia, pregnancy quality, osteoporosis, renal failure and n-3 omega PUFAs still requires further studies to be highlighted. Some algae species and dinoflagellates appear as potentially rich sources of n-3 omega PUFAs for the very near future although we have also got very limited number of researches in the related area. The greater effects of mega doses in some diseases have been advocated but the risk of side effects such as internal bleeding associated with such doses was neglected like the negligence of antioxidant administrations in many studies which should be combined with n-3 omega administration.

The effect mechanism of n-3 omega PUFAs on catecholamine metabolism, the daily recommended intakes for cancer, heart disease and diabet suffered patients, pregnant women, the elderly and children,

the type of n-3 omega PUFAs – LN, DHA or EPA or both, the stronger effect, possible serious side effects of n-3 omega PUFAs on patients with ventricular tachycardia and ventricular fibrillation and finally, the potential of n-3 omega PUFAs to ameliorate coronary arteriosclerosis after heart transplants are all the initial questions which still wait to be studied and answered. More studies are needed to define the status of n-3 omega PUFAs in food and nutrition science. The studies required to be performed in a very near future should rather be double blind, placebo controlled, large big scale, randomised and cohort prospective studies rather than case control in small scale.

Conclusions according to all of the literature findings mentioned in the book about the current status of cancer nutrition

- A standard diet cannot be created since it depends on the anti-cancer drug. So, the list of the foods which show synergism for the mentioned anti-cancer drug should have been determined, while the ones which show antagonism should have been eliminated.
- The lists of the foods for advise and the foods to avoid for each anti-cancer drug should have been exist as in catalogs in Oncology departments, dietary clinics while the patients should have been directed by oncologists by considering the foods synergistic with the anti-cancer drug administered.
- Some pathways and proteins are in dual functions, sometimes apoptotic, but sometimes anti-apoptotic, when, and why???. These dual functions are exploited by the anti-cancer drugs, thus, the bio-active compounds which will be advised for the drug, should have been determined according to this important detail!!!
- Yet, the creation of such anti-cancer diets are not so easy, since there are many signaling pathways, signaling proteins and enzymes that inhibit or induce cancer. Once, the foods, which inhibit these signalings, signaling proteins and enzymes which induce cancer, are combined with the drug, the anti-cancer diet may be created.
- Fructose can not be blamed as the only culprit while its precursor is glucose which has similar cancer inducing effects. Moreover, glucose, which can be converted into fructose during glycolysis, is exist in almost all foods.
- Blaming vegetables and fruits, like it is often done by the media about fruits because of their fructose content, is meaningless, cannot be correct, since the same fruits and many plant origin

foods have got many anticancerogenic bio-active compounds (minerals, vitamins, flavons and flavonoids..) besides fructose. In spite of glucose or fructose deprivation, cancer cells will continue to produce glucose more than before to adapt the glucose/fructose deprivation by using P2X7 receptor. So, Warburg effect hits the wall in cancer but the theory and findings of Amoroso et al. (2012) seem to work.

- Even a fatty meat, or a fried food, cannot be evaluated as completely harmful in the diet of the patient with cancer since it may produce ROS, like the ROS producing anti-cancer drugs and may even increase the anti-cancer potential of these drugs by increaing ROS production level. A fatty meat or a fried food may be evaluated as harmful in case of their rich consumptions by the people without cancer!!!, because they do not have got tumors to be killed by ROS, so the produced ROS may be redirected to healthy cells.

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