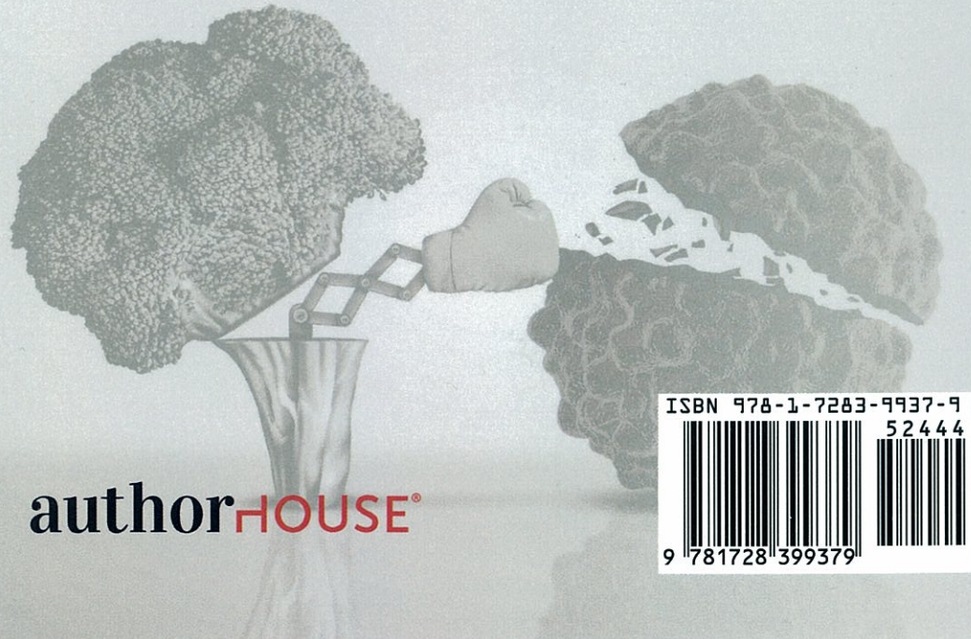
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PREFACE

Although a nutrition program for people and the patients with cancer has often been recommended, it is not more than cliché and standard recommendations like the foods with lower fat, and higher antioxidant, and fiber content. On the other hand, not only for cancer but for all other metabolic diseases, a diet and each of its components, foods, should be different and specific due to difference of the genes, pathways, enzymes and signaling and different effects of each food. For example, the inhibition of Akt/PI3K/Her2/TNF-α/EGFR triggers the apoptotic effect of FOXO3. Therefore, during the treatments with FOXO3 inducing chemotherapeutics, FOXO3 inducing as well as Akt/PI3K/Her2/TNF-α/EGFR inhibiting food/plant bioactive compounds and their rich foods should have been included into diet. On the other hand, one of the strongest antioxidants and anticancerogenic substances, resveratrol, might be contraindicated with the chemotherapeutics which inhibit IL6/STAT3/IL-8 since it induces IL-8. Ironically, ROS, the harmful inflammatory substances, might kill cancer cells. Therefore, a fatty hamburger or a high calorie candy food which is often considered as harmful might ironically be beneficial when consumed as combined with the ROS producing chemotherapeutics. Even the inflammatory Omega-6 PUFAs have inhibitory effect on the expressions of Metalloproteinases (MMPs) and might have enhanced the anticancerogenic effect of the chemotherapeutics which target MMPs. In the review which is the most comprehensive and only one of its kind, for now, the associations of each of the 79 food/plant bioactive compounds with each of the 28 cancerogenic pathways, signaling and enzymes were determined and listed by referring 1650 studies including cohorts, case-control studies, and theories.The main aim of the review is to design a diet which

is specific to chemotherapy as complementary for the first time to enhance anticancerogenic effect of the chemotherapy. Only such a diet may help to oncologist, dietician and patient with cancer for a better prognosis. It should never be disregarded that any of the food which is contraindicated with the effect of the chemotherapeutic agent on the signaling, pathway or enzyme would have to limit the expectation from the chemotherapeutic agent. Finally, the answer and validity of the question of 'should fructose-rich foods be blamed as the main culprit in cancer nutrition in spite of their significant anticancerogenic effects were discussed in detail. Finally, the book may be considered as complementary as a continue part of the previous book, entitled 'Map for Drug and Food in Cancer Nutrition' which was published by the same publisher. Differentially, this book analysed first time, the interactions of arginine, the signaling of Notch and Wnt, the genes; p21CDKN1A, p27 and p38, the MMR protein errors, ABC proteins, Omega-3 Poly Unsaturated Fatty Acids and the genes; Lin 28, Lin-7, the CD4 +T cells, Th17 cells, IL-22, IFN-Ɣ and fiber intake in daily nutrition with other food/plant bio-active compounds, cancerogenic genes, proteins, enzymes and pathways. Furthermore, the dual effect of Notch signaling, the satus of arginine in cancer progress and cancer therapies, the interactions of glucose, fructose and glutamine in cancer progress and cancer therapies and the Immunotherapy were reviewed first time in detail under the highlight of the current findings, based on case-control, cohort and review studies.

All the findings, the detailed review of the book, reaches one great result. Cancer creates its devastating effect by damaging the transfer of electricity while cancer itself is also formed by the damage in electricity and disordination of electricity. As long as we could find the ways to stop the abnormal, damaged electricity transfer (the cancerogenic signalings.) among the cells, enzymes, pathways and genes through the food/plant bio-active compounds and their cooperation with the chemotherapeutic agents and/or radiotherapy, then we could have a breakthrough to suppress the progress of cancer and increase the therapeutic effect of chemotherapy.

ABOUT THE AUTHOR

Ugur Gogus was graduated from Faculty of Veterinary in Ankara/ Turkey in 1986. He completed his doctorate in Meat Technology in Food Engineering Department of Faculty of Agriculture in Turkey in 1995. He has reviews, researches and books as related to food and antiaging, functional foods, meat hygiene, food microbiology and food safety. He has also several oral presentations in many countries including China and United States of America. He has been honoured with International Professional of the Year 2006 (International Biographical Centre, Cambridge/United Kingdon) and Great Minds of 21st Century (American Biographical Centre, USA, 2008). He has been working as teaching staff in Middle East Technical University, Vocational School of Higher Education, Turkey.

ABBREVIATIONS

VEGF:	Vaso Endothelial Growth Factor
TNF-α:	Tumor Necrosis Factor-alpha
NF-kB:	Nuclear Factor Kappa B
Hh:	Hedgehog
PI3K:	Phosphoinositide 3-kinase
Akt:	Protein kinase B, a serine/threonine specific protein kinase
mTOR:	Mammalian Target of Rapamycin
ROS:	Reactive Oxygen Species
HIF-α:	Hypoxia-Induciable Factor 1-alpha
MMP:	Matric Metalloproteinase
MDR:	Multi Drug Resistance
HO-1:	Heme Oxygenase-1
Her-2:	Human Epidermial GrowthFactor Receptor-2
FOXO3:	Forkhead Box O3
Bcl-2:	B-cell lymphoma 2 gene
PUMA:	The p53 upregulated modulator of apoptosis
Bax:	Bcl-2 Associated X protein
COX-2:	Cyclooxygenase-2
IL-6:	Interleukin 6
STAT-3:	Signal Transducer and Activator of Transcription-3
IL-8:	Interleukin 8
PD-1:	Programmed cell Death protein-1
PD-L1:	Programmed cell Death protein Ligand-1
GRP78:	The unfolded protein response inhibitor 1

Herp:	a chaperon
P21:	Cyclin-dependent kinase inhibitor 1
AP-1:	Activator Protein 1
P38:	a mitogen activated protein linase (MAPK)
MMR:	Mismatch Repair
MDR:	Multidrug Resistance
P-gp:	P-glycoprotein
CD4 +T cells:	The T helper cells.
XAF1:	X-linked inhibitor of Apoptosis-Associated Factor 1
Ptch1:	Patched 1
Smo:	Smoothened
PIP3:	Phosphatidylinositol 3,4,5-triphosphate
ERK 1/2:	the extracellular signal-regulated kinases 1 and 2
ECM:	extracellular matrix
TIM-2:	Tissue Inhibitor of Metalloproteinase
Gpx:	glutathione peroxidase-1
GHS:	glutathione
SOD:	Superoxide dismutase
Nrf2:	Nuclear factor erythroid-derived 2
JNK 1, 3:	c-Jun amino-terminal kinases 1 to 3
CRP:	C-Reactive Protein
EGF:	Epidermial Growth Factor
Keap 1:	Kelch-like ECH associated protein 1
ARE:	antioxidant response element
TRAIL:	TNF-related Apoptosis Inducing Ligand
RICTOR:	Rapamycin-Insensitive Companion of mammalian Target of Rapamycin

Important note: All through the manuscript, the parentheses which include the author and date are the studies which confirmed or determined the anticancerogenic effect of the drug or bioactive compound.

1

INTRODUCTION TO THE DESIGN OF THE SPECIFIC NUTRITION FOR CHEMOTHERAPY (AND/OR RADIOTHERAPY)

Owing to its huge complexity in progress due to many different reactions, pathways, signaling and proteins, and a great number of food/plant bioactive compounds with their different and unique effects on these biochemical reactions, the necessity to clarify the interactions of the bioactive compounds with these cancerogenic signaling, enzymes and pathways, have become more crucial than ever. In spite of the chemotherapeutic agents namely, sunitinib, sorafenib, 17-AAg, thapsigargin, eeyarestatin, bortezomib, metformin, tunicamycin, versipelostatin, brefeldin A, honokiol, paclitaxel, fulvestrant, doxorubicin, DBeQ, MKC-3946, MAL3-101, tamoxifen, nafoxidine, C1628, MG-132, reolysin and many others, with their well defined effect mechanisms and involvements in cancerogenic pathways, their interactions with the bioactive nutrient compounds like I3C and lycopene, have not been properly reviewed. However, the design of an anti-cancer diet for a patient with cancer during the treatment, can only be made according to the interactions between the anti-cancer drug and the bioactive compounds in the food. Each drug and each bioactive compound has different effects on the cancer triggering signalings; GRP78/BIP, beta catenin, Nrf2-keap1, ERK, Hedgehog, Rb/E2F, notch, PI3K/AKT/mTOR; the cancer triggering or inhibiting proteins; TNF, p38, p23, Bcl, GRP78, NF-kB, CDK, STAT3, Bax, MMP, Fas, erbB2, Foxo3, G6DP, STEAP, SOX2, galectine 3, CDC25, COX2, caspase, E2F3, AR, PRDX3, ERalpha, iNOS, PRDX3,

IGF-1, HO-1, VEGF, GATA3, IL-1B, and the enzyme systems; H_2O_2 fenton, Nrf2/phase II and CYP. Therefore, the first step to design an anticancer diet as specific to chemotherapy should be the determination of the bioactive nutrient compounds which have the same effect with anti-cancer drug on these proteins, enzyme systems or signaling. The strategy to 'what to eat and drink' during cancer and cancer therapies, can only be made by knowing and combining the bioactive compounds and their food sources and the anti-cancer drug, both of which synergistically affect the same pathways, proteins and/or signalings. For example, Tumour Necrosis Factor, TNF, may act as tumor enhancer in some cases. One of the anti-cancer effects of kaempferol (a flavonoid) is to inhibit TNF, like the anti-cancer drugs; infliximab, adalimumab, narasin, honokiol, vorinostat, tribromsalan, bithionol and celecoxib. During such treatments, the flavonoid and also some other food/plant bioactive compounds with the same effect, namely, curcumin and resveratrol, and their rich sources, should be exist in the anticancer diet so that the group of chemotherapeutic agents which inhibit TNF and the food/plant bioactive compounds might form a synergism for a much stronger inhibition on the protein. Opposite, arginine and/or nitric oxide treatments and supplementations and their rich sources, namely, egg white, turkey breast, beef and ground red meat should be avoided since arginine and NO activate both TNF and NF-kB and may inhibit the anticancerogenic effect of the treatments which administer TNF/Nf-kB inhibitors. Quercetin, one of the most powerful antioxidant bioactive compounds, may not be beneficial in every chemotherapy. If the chemotherapeutic agent targets cancer cells by inhibiting PI3K/Akt/mTOR pathway and Hg signaling, then quercetin and its rich food/plant sources might be useful since the flavonoid inhibits the same cancerogenic pathway and signaling. But, if the chemotherapy aims to target cancer cells by inhibiting VEGF and HIFα, the flavonoid and its rich food/plant sources should be avoided since it induces VEGF and HIFα. Omega 3 PUFAs which are often recommended as indispensable elements of a healthy and antiaging diet might be contraindicated with chemotherapy if the chemotherapeutic agent kills tumor cells by inhibiting the chaperons, GRP78 and Herp, and the immune cells, CD4 +T, since the fatty acids induce GRP78, Herp and CD4 +T cells. Similarly, if the chemotherapeutic agent aims to inhibit the copy transfer from CD4 + T

cells into tumour cells, the fatty acids and the amino acid which is important for immune system, amygdalin, should better be avoided since the fatty acids and amino acid activate the expression of CD4+ T cells. On the other hand, it shoud never be disregarded that the exclusion of Omega 3 PUFAs and amygdalin is an exception and can only be correct for the chemotherapy with GRP76, Herp and CD4 + T cell inhibitors. In other conditions, both of the amino acid and fatty acids are essential for a healthy immune system as well as cardiovascular system. Briefly, the determination of the foods in an anti-cancer diet can only be made by analyzing the bioactive nutrient compound and anti-cancer drug interactions. Therefore, the interactions of each of the bioactive nutrient compounds and their food sources, with each anti-cancer drug, were analyzed and documented in the most comprehensive review in the field of cancer nutrition. Accordingly, the associations and interactions of totally 79 food/plant bioactive compounds: resveratrol, EGCG, kaempferol, genistein, lycopene, apigenin, amydgalin, Omega 3 PUFAs, vitamin D3, α-tocopherol, ascorbic acid, curcumin, baicalein, daidzein, I3C, β-carotene, arginine, sulforaphane, folic acid, δ-tocopherol, gingerol, silymarin, berberine, turmeron, Omega 6 PUFAs, myricetin, choline, B12, chlorophyll, α-crypthoxhanthin, zeaxhanthin, egg derived peptides, lutein, wagonin, luteolin, trigonellin, retinoic acid, chrysin, brusatol, capsaicin, piperine, enterolactone, matairesinol, laiciresinol, esculetin, glutamine, NO, campanulin, astaxanthin, theophylline, caffeine, rotundarpene, Υ-tocotrienol, berberine, hesperetin, naringenin, elemental calcium, diosmin, prostratin, myricetin, Δ-tocotrienol, isorhamnetin, lupeol, chlorogenic acid, procyanidin A2, B2, vitamin B6, biochanin A, silibinin, tangeretin, vitamin E succinate, icaritine, wagonin, morin, coumarin, sesquiterpenes, limonene, theophylline and rotundarpene, with the most common pathways, signaling and enzymes in cancer progress, were analyzed and discussed in detail by evaluating 1650 studies. The interactions of these food/plant bioactive compounds with totally 28 proteins, signaling, enzymes (ROS, Hg, PI3K/ mTOR, VEGF/HIF-α, MMP, TNF-α, Nrf2, MDR, HO-1, Her2, mTOR, Foxo3, Bcl-2, PUMA/ Bax, Cox-2/Nf-kB, IL-6/STAT3, IL-8, Notch, Wnt/B-catenin, Lin 28, PD-1/PD-L1, GRP78/Herp, p21, AP-1, p38, MMR, MDR/P-gp/ABC, and CD4 +T), were analyzed. As a result, an anti-cancer diet for each group

of anti-cancer drugs, in which both the diet and drug/drugs target the same pathway/pathways, protein/proteins and/or enzyme systems, could have been designed for the first time. There are many scientists and teams all over the world with the same aim, to find out a therapeutic solution to cancer by analyzing the mentioned cancerogenic signaling, pathways and enzymes and their interactions with the food/plant bioactive compounds. But, either these people or their published studies are so disconnected that most of their findings can not reach a final point to be adapted into practice in clinic nutrition and nutrition therapy. Moreover, the cliché diet recommendations still predominate the media, treatments and hospitals. For all these reasons, the biggest aim in this mega review is to create a first time design of cancer nutrition as specific to chemotherapy by gathering and connecting the findings of 1650 studies which are consisted of cohorts, case control studies and theories. During the mega analysis of the associations and interactions of the chemotherapeutic agents with the proteins, pathways and signaling, the significant factors which effect the cancerogenic and anticancerogenic potential of the drug and food/plant bioactive compound were also discussed. For example, some of the most important reasons of the conflicting results in many cohorts might occur due to 'dose', like, 'high dose arginine and NO (>400 μM) concentrations have a strong anti-cancer effect', while the lower doses are ineffective. In the last part followed by criticizing the answer and validity of the 'question of 'should fructose rich foods be categorized in high risk category in cancer only because of their rich fructose contents?', the cohorts to highlight the effect of some of the most common food / plant bioactive compounds on various cancer types were discussed with their important points and drawbacks. Finally, the studies and answers which are needed to strengthen the improving effect of the anticancer diet which is specific to chemotherapy were declared.

1.a. The association of glutathione, catalase, fructose and Reactive Oxygen Species (ROS) with food and cancer

Reactive Oxygen Species (ROS) are generated by oxidant enzymes, phagocytic cells and ionizing radiation while their production is induced by a free radical. Superoxide anion (O_2^-) is the first free radical which

is formed by the electron transport chain when O_2 picks up a single electron. Other reactive substances like hydroxyl (OH), perhydroxyl (HO_2) and hydrogen peroxide (H_2O_2) are formed by the superoxide anion (O_2^-) (Nappi and Vass, 1998). The superoxide anion (O_2^-) enters into a reaction to form hydrogen peroxide (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 to form highly reactive and very harmful hydroxyl radical (OH) by interacting with metals such as Fe^{2+} and Cu^+. The initial reason for cancer formation due to the reactive species might be the elevated levels of modified bases in DNA, like the substitution of CC to TT which is caused by the harmful end product of H_2O_2, hydroxyl (OH) (Reid and Loeb 1993). The reactive and harmful hydroxyl radical (OH) from the harmless H_2O_2, is one of the critical points that indicates to the role of antioxidants and antioxidant rich foods like fruits and vegetables, since the pro-oncogenic H_2O_2 can be neutralized by the antioxidant enzymes, catalase and glutathione peroxidase, in these products. The neutralization of H_2O_2 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 later phase, 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 and prevents 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). Another antioxidant, glutathione peroxidase, catalyzes the pro-oncogenic hydroxyl radical (OH), yielding GSSG (oxidized glutathione), water and alcohol (Toppo et al. 2009). Thus, the foods which are rich in catalase or glutathione peroxidase may contribute to prevent from the risk of cancer. This means that the foods whose rich catalase and/or glutathione contents were determined by the researchers in the following parentheses; 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) and spinach (Sheptovitsky and Brudviq 1996), might

help to cancer prevention with the inhibitory effect of their catalase and glutathione contents on H_2O_2 and OH. On the other hand, the first dilemma about evaluating the cancerogenic potential of a food appears if only the fructose contents are taken into consideration. For example, when the rich fructose contents of onion, Brussels sprout, potato, carrot, cabbage and spinach as 1280 mg/160 g, 930 mg/88 g, 340 mg/369 g,1000 mg/15 g, 1480 mg/89 g, 150 mg/30 g (Nutritiondata 2018), respectively, are concerned, should they be categorized in high risk category in cancer only because of their rich fructose contents in spite of their rich glutathione and catalase activities?.

The close relation of ROS with the risk of cancer and the cancerogenic effect of signals of ROS in cell proliferation and tumor progression have often 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 aging and disease, the present data indicates to a dual effect of ROS in cancer progress. The higher concentrations of ROS, when combined with the anti-cancer treatments which aim to kill cancer cells by generating these radicals, can destroy cancer cells. The following treatments can be considered as the examples of the anticancerogenic and apoptotic effect of ROS. These are; 'the damage by the irradiation on Burkitt lymphoma B and epithelial breast cancer cells' (Minai et al. 2013), 'ROS-induced 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 'ROS that are induced by 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)' and 'ROS which is induced by Ras' as combined with the enzyme, NOX4 (NADPH oxidase 4) and their damage on PDAC (pancreatic ductal adenocarcinoma) cells (Ogrunch et al. 2014), and finally, 'the damage of the administration of reactive oxygen and reactive nitrogen species (ROS/RNS) which is generated by atmospheric pressure air plasma on the cervical cancer HeLa cell' (Ahn et al. 2014). Furthermore, another apoptotic effect of ROS is due to their interaction with the genes which regulate apoptosis (programmed cell death), like in Rotenone.

The chemotherapeutic agent kills cancer cells by decreasing the antiapoptotic protein, Bcl-2, and increasing the apoptotic protein, Bax, while inactivating the antiapoptotic gene, ERK1/2 (serine/threonine kinase) as in a ROS dependent manner (Deng et al. 2010; Stanciu et al. 2000; El-Najjar et al. 2010). The apoptosis which is induced by ROS does not occur only by some of the chemotherapeutic agents, but also some bioactive food compounds such as sulforaphane. The bioactive compound, as one of the most commonly known anti-cancer substances which is abundant in cruciferous vegetables, alters mitochondrial membrane potential by the influx of ROS which is generated by the inducing effect of the isoflavon on these radicals (Telomerase Reverse Transcriptase which repairs the defects in the chromosoms) (Choi et al. 2008; Meeran et al. 2010). The generation and influx of ROS by sulforaphane trigger the proapoptotic protein, Bax, while Bax permeabilizes the outer mitochondrial membrane, leading to release of cytochrome c and Caspases, the proapoptotic cystein-dependent aspartate-directed proteases or cysteine-aspartic proteases, all of which result in apoptosis (Hsu et al. 1997; Antonsson et al. 2001; Li et al. 1997). On the other hand, the chemotherapeutic agents whose anticancerogenic effects due to their inductions on ROS and Caspases were determined by their references in the following 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 and Ando 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 which are responsible for many metabolic diseases, aging and cancer, the 'ROS', are exploited by some of the present anti-cancer

drugs to kill cancer cells. Confirmingly, the possibility of the stronger antiproliferative effect of the combination of the chemotherapeutic agent, fenretinide, and I3C, might have been due to the generation of ROS by the combination of I3C and fenretinide. It seems clear that the synergism of the food bioactive compound and chemotherapeutic agent increases the total amount of ROS to enhance the apoptotic effect on cancer cells (Hwang et al. 2011; Shimamoto et al. 2011; Bai et al. 2013). On the other hand, 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. The phosphorylation of ERK1/2 activates caspase-9, -3 and -8 (Park et al. 2013) and increases the expression of XAF1. The activation of the caspases and the overexpression of XAF1 increase the sensitivity of cancer cells to apoptosis (Plenchette et al. 2007) while inducing the translocation of proapoptotic protein, Bax, into mitochondria. Briefly, the latest findings clearly indicate a close and significant link among the proapoptotic proteins Bax, ERK1/2, Caspases, ROS and XAF1 during apoptosis. Such a link which leads to apoptosis might also have been 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).

1.b. The chemotherapeutic agents and the food/plant bioactive compounds that target cancer cells by inducing ROS

The formation of reactive oxygen species (ROS) and as a result the induction of caspase activity which causes apoptotic effect have also been determined for many other important bioactive compounds. These food bioactive compounds whose anticancerogenic effects due to their inducing effect on ROS were determined with the references in the following paranthesis are as follows. These are, resveratrol (150 μM/24h on the colon cancer cell lines; HT-29 and Colo201 and 200 μM/24h on human lung cancer cell lines; A549 and H460) (Miki et al. 2012; Guha et al. 2011), EGCG (500 μM/24h and 500 μM/30min, in human mesothelioma cells, 50 μM/24h, in human lung cancer cell lines; MRC-5 and WI-38) (Satoh et al. 2013; Ranzato et al. 2012; Lu et

al. 2013), kaempferol (100 μM/3d, in IL-1β-stimulated osteoclasts, 50 μL24h, in non-cancerous esophageal cell line, CHEK,1 and 40 μM/24h, in ovarium cancer cell line, OVCAR-3) (Lee et al. 2014; Halimah et al. 2015 and Luo et al. 2010), genistein (50 μM/96h, in breast cancer cell lines; MDA-MB-231 and MDA-MB-468)(Ullah et al. 2011), quercetin (100 μM/12h, in breast cancer cell line; MDA-MB-231, hepatoma cell line; SKHepl and lung cancer cell line; A549) (Lee et al. 2015), lycopene (4 mg/Kg/d by gavage for 30 d in rats, 10 μM/24h, in prostate cancer cell line; LNCaP, PC-3 and colon cancer cell line; HCT-116) (Krishnamoorthy et al. 2013; Palozza et al. 2010), apigenin (60 μM/48h, in human neuroblastoma cell line, NUB-7) (Torkin et al. 2005), vitamin C (20 μM/24h, in human gastric cancer cell line, AGS) (Lim et al. 2016), amygdalin (10 mg/mL, in prostate cancer cell lines; DU145 and LNCaP) (Chang et al. 2006), Omega 3 fatty acids (200 μM/72h DHA or EPA, in human breast cancer cell line, MCF-7, 100 μM/72h DHA or EPA, in the human pancreatic cancer cell lines, MIA-PaCa-2 and Capan-2) (Kang et al. 2010; Fukui et al. 2013) and vitamin D (calcitriol, 100 nM/24h, in the human breast cancer cell line, MCF-7) (Weitsman et al. 2003). Therefore, these food bioactive compounds and their rich sources may be beneficial to enhance the apoptotic effect of the chemotherapeutic agents which target cancer cells by creating a synergism to generate more ROS and as a result more apoptotic effect. These drugs and bioactive compounds may also form a synergism not only to kill cancer cells via the induction of ROS but also to the activation of the expressions of Bax, ERK1/2, caspases, and XAF1, all of which triggered by ROS.

1.c. The food/plant bioactive compounds which might be contraindicated with the chemotherapeutic agents that target cancer cells by inducing ROS

But, the vitamins; folate, B_6, tocopherol and their rich nutrition might have been contraindicated with the mentioned ROS producing chemotherapeutic agents/food bioactive compounds because of the following reasons. First, toocopherol and ascorbic acid may be useful except the anticancer treatments with the mentioned chemotherapeutic agents and food/plant bio-actice compounds which kill cancer cells

by producing ROS. In the metabolism of tocopherol, followed by the absorption of the vitamin and its arrival to cell membrane, 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 radical can be reduced to tocopherol by vitamin C. The combined administrations of tocopherol and vitamin C can compensate for decline in the important anticancerogenic antioxidant, glutathione (Lenton et al. 2003; Shklar et al. 1993) and this may be a reason for the stronger antioxidant capacity of 'ascorbic acid and tocopherol' combination. Another reason for the necessity of the combined use of both vitamins is that, ascorbate (a vitamin C form) and alpha/gamma-tocopherol are water soluble and fat soluble antioxidants which interact and work synergistically 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. For these reasons, either the combined administrations of vitamins may decrease the level of ROS production, especially OH- and O2-, the oxidant radicals which have significant destructive effect on tumour cells. Although there are some studies which claim the cancerogenic effect of vitamin E (tocopherol), like the ones belong to Chen et al. (2015) and Klein et al. (2011), they neglect to study the anticancerogenic potential of the combined use of vitamin E with other vitamins and minerals, e.g. vitamin C. On the other hand, the very rich consumption of B_{12}, folate and B_6 cause the polymorphism of the enzyme, methylentetrahydrofolate reductase (MTHFR) C677T, the enzyme which catalyzes the irreversible conversion of 5,10-methylenetetrahydrofolate to 5-methylenetetrahydrofolate which is crucial in DNA synthesis. During polymorphism of MTHFR C677T due to either hypomethylation by folate/B_6 poor nutrition or hypermethylation by rich folate/B_6 nutrition, 5,10-methylenetetrahydrofolate can not be converted to 5- methylenetetrahydrofolate which results in the increase

of 5,10-methylenetetrahydrofolate (homocysteine) (Kim 2003). The excess amounts of homocysteine incorporate with uracil in DNA, and this incorporation form chromosomal breaks and uracil defects in DNA (Christman et al. 1993) which is one of the main reasons of colon cancer (Ames 2001). Although, 20 μM and higher concentrations of homocysteine are informed to increase ROS (Curro et al. 2014), the risk of the chromosomal breaks and urasil defects might worsen the prognose during the treatments with ROS generating chemotherapeutic agents. Therefore, both folate/B_6 with its risk of the uracil defect, and the combination of tocopherol and ascorbic acid with its antioxidant and inducing effect on glutathione which may reduce ROS generation, might have been contraindicated with the mentioned chemotherapeutic agents and food bioactive compounds which kill cancer cells by producing ROS.

2

HEDGEHOG SIGNALING AND ITS RELATION WITH CHEMOTHERAPEUTIC AGENTS AND FOODS

The Hedgehog signaling is a signaling pathway that transmits information with Hedgehog proteins, the polypeptide ligands, to embryonic cells. The polypeptide ligands were first discovered in fruit flies of the genus *Drosophila* and the intercellular signaling molecule was called 'hedgehog'. The mutations of the molecule were responsible for spike and hairy formations of denticles in the larvae instead of normal proteins. Its pathway and important effects of its mutations were first discovered in 1980 (Scales and de Sauvage 2009; Nüsslein-Volhard and Wieschaus 1980). The signaling pathway begins with binding of Hedgehog (Hh) to Patched (Ptch1), the receptor of a 12-transmembrane morphogen, a soluble molecule which inhibits the activity of another transmembrane protein, Smoothened (Smo). The binding of Hh to 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 which 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 the aberrant Hh signaling' and cancer, is well documented in small cell lung cancer, pancreatic cancer, prostate cancer, medulloblastomas, leukemias and basal cell carcinomas (Jiang and Hui 2008; Wang et al. 2013; Atwood et al. 2012; Hahn et al. 1996; Xie et al. 1997; Hettmer et al. 2013).

2.a. The chemotherapeutic agents and food/plant bioactive compounds that target cancer cells by inhibiting Hedgehog

The following chemotherapeutic agents are the ones whose anticancerogenic effects by inhibiting the signaling were confirmed by the references in the following paranthesis. These agents are; veratramine (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), MRT-92 (Hoch 2015), soridegib (IPI-926) (in advanced solid tumors) (Jimeno et al. 2013), phthaladines, namely LY2940680, NVP-LEQ506 (Karhadkar et al. 2004), itraconazole (an antifungul, often administered in meddulloblastoma) (Kim et al. 2010), TAK-441 (Kogame et al. 2013), XL-139 (Tremblay et al. 2009), HTS piperidines (Yuan et al. 2007; Berman 2003), MRT-83 (Roudat et al. 2011), PF-04449913 (in acute myeloid leukemia) (Fukushima et al. 2013), N-acylethanolamides, 2-acylglycerols and 2-alkylglycerol (endocannabinoids) (Khaliullina et al. 2015). On the other hand, the food/plant-bioactive compounds whose inhibitory effects on the signaling were confirmed by the researches in the following paranthesis and their rich sources are; resveratrol and resveratrol rich sources like grapes, blueberries, raspberries, mulberries and red wine (Lyons et al. 2003; Vitrac et al. 2005) (resveratrol, 55 μmol/L/48h, in the gastric cell line; SGC-7901) (Stervbo et al. 2007), genistein and genistein rich foods like, currants, raisins, satsumas, Brazil nut, chestnut, coconut, bazelnut and sesame seeds (Liggins et al. 2000) (genistein, 10 μg/mL/48h, in the gastric cancer cell lines; AGS and MKN45) (Yu et al. 2014), curcumin and curcumin rich foods; turmeric and ginger (Tayyem et al. 2006) (curcumin, 50 μM/7d, in the human bladder cancer cell line, UM-UC-3) (Wang et al. 2017), EGCG (Epigallocatechin gallate) and EGCG rich foods like 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) (EGCG, 25 μM/21d as combined with a phosphodiesterase 3 inhibitor, PDE3, in the pancreatic

cancer cell lines; Panc-1, BxPC-3 and MIAPaCa-2) (Kumazoe et al. 2017), apigenin and apigenin rich foods like; parsley and celery (Manach et al. 2004) (Apigenin, 40 μmoL/L, in the human ovarian cancer cell line, SKOV3) (Tang et al. 2015), baicalein rich foods/plants like; *Scutellaria baicalensis* (or Huang Qin, also known as the Chinese skullcap), carrot, celery and broccoli (Varsha et al. 2017) (baicalein, 256 μM/72h, in the human pancreatic cancer cell lines; PANC-1, BxPC-3 and SW1990) (Song et al. 2018), quercetin and quercetin rich foods like onions, kale, broccoli, lettuce, tomatoes, asparagus, red leaf, lettuce and green pepper (Jin et al. 2011; Reay and Lancaster 2001; Neto 2007; Lee et al. 2013 and Plumb et al. 1999; Lam et al. 2010; Nishimuro et al. 2015; Slusarz et al. 2010), (quercetin, 80μM/72h, in the human breast cancer cell line; MDA-MB-231) (Nguyen et al. 2017) and D_3 or/and calcitriol supplements or/and vitamin D rich foods e.g. cod liver oil, swordfish, salmon, tuna fish, orange juice-fortified, yogurd-fortified, sardine, mackerel, mushroom, liver, beef, egg, cheese, margarine-fortified (USDA National Nutrient Database Release 28) (calcitriol, 10 μM/48h, in murine basacl carcinoma cells) (Tang et al. 2011). Therefore, a diet rich in these bioactive compounds with their food sources might enhance the anticancerogenic potential of the mentioned drugs and chemotherapeutic agents with a synergism via the inhibition of the signaling. The signaling is induced by ROS (Romero et al. 2018). But, this time an important question arises. Most of the food/plant bioactive compounds that target cancer cells by inducing ROS, e.g. resveratrol, EGCG, genistein, quercetin, lycopene, apigenin, Omega 3 polyunsaturated fatty acids (PUFAs) and vitamin D are the food/plant bioactive compounds which inhibit the signaling in spite of the fact that ROS induce the signaling. The only explanation might be due to another different mechanism might have been involved rather than 'the induction of the signaling by ROS'. It should be noted that, although red wine is rich in resveratrol, it is the antagonist of the drugs and food bioactive compounds above because of its inducing effect on the signaling (Bai et al. 2014, Mo et al. 2011; Gao et al. 2015).

3

THE SYNERGISM AMONG HIF-1ALPHA, PIP3, PI3K, ROS, ERK1/2, VEGF AND AKT AND THEIR PATHWAYS TO INDUCE CANCER

VEGF, a signal protein, is produced to stimulate vasculogenesis and angiogenesis. Hence, it is considered as one of the initiators 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). Another signaling, PI3-kinase/Akt, is involved in protein synthesis, proliferation and survival. Besides VEGF and PI3K/Akt, one of the other contributers to cancer progress is HIF-1α. Significant regions of cancer often grow in hypoxic conditions since they have not any functional vasculature in a highly proliferative tumor mass (Eales et al. 2016; Brahimi-Horn and Pouyssegur 2007). So, the creation of a hypoxic media may be considered as a kind of adaptation of cancer cells to insufficient vascularization. HIF-1α is the inducible subunit of the HIF-1 transcription factor that regulates genes which are involved in the response to hypoxia, some of which promote neovascularity. On the other hand, VEGF is one of the genes which is upregulated by HIF-1.

This is also confirmed by the decrease of VEGF mRNA as a result of HIF1α extermination (Lin et al. 2004). The same close relation between VEGF and HIF-1α is also exist between VEGF, HIF-1α, PI3K and p-Akt. PI3K signaling, the antiapoptotic signaling like Hh, is important in proliferation and cell-cycle progression and the signaling is activated by VEGF (Jiang and Liu 2009). Phosphatidylinositol 3,4,5-triphosphate (PIP3), the important lipid second messenger which is generated by PI3K with its vital role in several signal transduction pathways, is dephosphorylated by PTEN, an antagonist of PI3K, and as a result, PI3K signaling is regulated (Chalhoub and Baker 2009). PTEN also decreases the expression of ERK1/2 in several malignancies (Chetram and Hinton 2012). On the other hand, there is a close relation between ERK1/2 and VEGF and both genes induce each other (Ye et al. 2010). The induction between ERK1/2 and VEGF also triggers Akt, (also known as protein kinase B), the serine/threonine kinase and the key regulator of cell proliferation and survival, which is often dysregulated in human cancers. The kinase acts as oncogenic and responsible for tumorigenesis in PTEN deficiency (Rosen and She 2006). In a nutshell, the activation of VEGF by PI3K/Akt (Kitamura et al. 2008), like the Akt activation by ERK1/2 and VEGF, should be considered as the crucial contributors to cancer progress. Therefore, HIF-1alpha, PIP3, PI3K, ERK1/2, VEGF and Akt and their signaling pathways (Figure 1), as in a close synergism, is a critic point in cell proliferation and cancer progress. The 'limitation in nutrient intake', 'lack of oxygen supply' and 'low pH' have often been appeared as the most important intrinsic stress factors which induce the 'PI3K/Akt/HIF-1α/ ERK1/2, VEGF' pathway, leading to tumor progess (Porta et al. 2014).

3.a. Nutrition and its association with PI3K, PI3K/Akt/mTOR/HIFα and VEGF

During the progress of cancer, the suppression of PI3K causes apoptosis by increasing Ca^{2+} release and inhibiting inositol activity while increasing platelet activity and elevating cholesterol and calcification due to the inositol inactivation. Accordingly, the critical point here is

the necessity of the protection of the patient who is administered PI3K inhibitors from the risk of high cholesterol rich foods and calcification which is caused by the high calorie foods. Instead, a nutrition which is low in cholesterol and calorie should be followed.

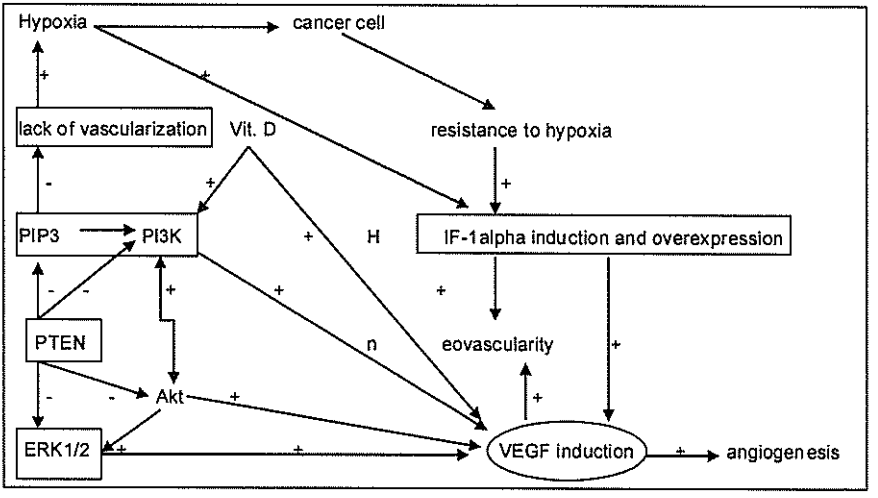


Figure.1 The synergism among HIF-1alpha, PIP3, PI3K, ERK1/2, VEGF and Akt and their signaling pathways/ +:induces -:inhibits

The inhibitors whose anticancerogenic effects due to their inhibitory effects on the PI3K/Akt/mTOR/HIF-1α/ ERK1/2 pathway were determined by the references in the following paranthesis are as follows. These are; wortmannin (Teranishi et al. 2009), piceatannol (Kwon et al. 2012), IC-87114 (Billottet et al. 2006), LY294002, PIK-75 (Jeong et al. 2014), XL-147 (Foster et al. 2015), 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), 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. 2014),

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), sunitinib, sorafenib (Krusch et al. 2009), paclitaxel, 17-AAG (Sain et al. 2006), tamoxifen (Chen et al. 2013), B1G1 (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). On the other hand, they might have had stronger anticancerogenic potential if they are administered during an anticancer diet which is rich in apigenin and quercetin. 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). Apigenin also reduces the phosphorylation of Akt, while increasing the binding of FOXO3a, a transcription factor whose disregulation is involved in tumorigenesis, as in close relation with p27 (a cyclin-dependent kinase inhibitor) which results in GO/G1-phase cell cycle arrest (apigenin, 50 μg/d for 6 days a week for 20 weeks in mice, in the prostate cancer cell lines; PC-3 and LNCaP) (Shukla et al. 2014). Similarly, quercetin induces apoptosis by inhibiting HIF-1α and VEGF (quercetin, 100 μM/8h, in the pancreas cancer cell line, LNCaP and breast cancer cell line, SkBr3); (Lee and Lee 2008). Therefore, the two bioactive compounds might enhance the anti-cancer potential of both PI3K, VEGF, HIF-1α and Akt inhibitors. On the other hand, the food/ plant bioactive compounds which inhibit VEGF and angiogenesis are; genistein and genistein rich foods (genistein, 10 mM/48h, in the human aortic endothelial cells (HAECs) (Si and Liu 2009), apigenin and apigenin rich sources (apigenin, 100 μM/72h, in the human breast cancer cell line, SKBR 3) (Seo et al. 2015), ascorbic acid and its rich sources (ascorbic acid, 1 mM/12h, in the murine melanoma cell line, B16F10) (Kim et al. 2011), I3C and I3C rich foods (I3C, 250 μM/24h, in the human endothelium-derived permanent cell line, EA hy926) (Wu et al. 2005), kaempferol and kaempferol rich foods (kaempferol, 25 μM/24h, in human retinal endothelial cells, HRECs) (Xu et al. 2017),

EGCG and its rich sources (EGCG, 500 μM/48h, in the esophageal squamous cell carcinoma cell line, Eca-109) (Liu et al. 2015), sulforaphane and its rich food sources (sulforaphane, 50 μM/6h, in the human colon cancer cell line, HCT116 and human gastric cancer cell line, AGS, important note is that sulforaphane inhibits both VEGF and HIF-1α) (Kim et al. 2015), beta carotene and its rich sources (beta carotene, 10 μM/24h, in HUVECs) (Dembinska-Kiec et al. 2005), ginger (*Zingeber officinale* Rosc) (active compound; gingerol 100 μg/mL/120h, in the ovarian cancer cell lines; CaOV3 and ES-2) (Rhode et al. 2007), artesunate (Chinese wormwood) (a semi-synthetic derivative of artemisinin which is extracted from the Chinese herb, *Artemisia annua*, ≥2 μmoL/L/48h, in the myeloid leukemia cell line, K562) (Zhou et al. 2007), resveratrol and its rich sources (resveratrol, 50 μM/24h, in human retinal pigment epithelial cells) (Nagineni et al. 2014), curcumin (its source; turmeric, *Curcuma longa*) (curcumin, 80 μM/48h, in the hepatocellular carcinoma cell line, H22 HCC) (Pan et al. 2018), 4-hydroxyderricin (*Angelina sinensis* extract, Dang Gui, 0.25 g/Kg/3d intraperitoneal injection) (Cheng et al. 2017), taxol (plant source is *Taxus brevifolia*, Pacific yew, 20 mg/Kg intraperitoneal injection sole or as combined with SC-560 or celecoxib) (Li et al. 2013), baicalein (plant source; *Scutellaria baicalensis*, baicalein, 100 μM/24h as combined with docetaxel, 10 nM, in anaplastic thyroid cancer cells) (Park et al. 2018), silymarin (its plant source is milk thistle, silymarin, 60 mg/Kg/12d oral supplementation as combined with doxorubicin in cardiac tissue) (Attia et al. 2017), honokiol (its plant source; *Magnolia* seed, honokiol, 20 μM/48h, in the human renal cancer cell lines; 786-O and Caki-1) (Banerjee et al. 2013), clausenidin (its plant source; *Clausena excavate* Burm.f., clausenidin, 50 μg/mL/24h, in the hepatocellular cancer cell line, HepG2) (Waziri et al. 2018), berberine (its plant source; *Coptis chinensis*, berberine, 200 μM/48h, in the human non-small cell lung cancer cell line, NSCLC A549) (Li et al. 2018) and the extracts of *Eugenia jambolana*, *Musa paradisiaca* and *Coccinia indica*, 200 μg/mL, in the breast cancer cell lines; MCF-7, MDA-MB-231(Harsha Raj et al. 2017). If these food/plant bioactive compounds and their rich sources are followed during the chemotherapic agents mentioned above, the synergism between them via the inhibition of VEGF might increase

the anticancerogenic potential of these VEGF inhibitors. It may significantly be important to note that, one of the most important factors which might have affected affect the anticancerogenic potential of resveratrol via the inhibition of PI3K and VEGF is the 'pH level'. Acidic pH promotes the growth inhibition, apoptosis and DNA damaging capacity of the bioactive compound 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) (Aggarwal et al. 2004), may be advised in diet as combined with resveratrol and resveratrol rich foods as long as the patient with cancer is free of reflux. When the effect of toocopherol is considered, it may be crucial that δ-T3 (delta tocotrienol) has an inhibitory effect on VEGF while α-T3 has no effect (δ-T3, 30 μg/L/72h, in HUVECs) (Shibata et al. 2009). The important detail about L-arginine and its association with VEGF is that low concentrations, ≤0.5 mmoL/L, promote the growth of cancer cells by up-regulating VEGF and COX-2 under the influence of NO, but high concentrations, ≥32 mmoL/L, induce apoptosis via NO by up-regulating of the apoptotic protein, bax, while down-regulating of anti-apoptotic proteins, p53, bcl-2 while inhibiting VEGF) (Huo et al. 2010). The status of vitamin D is also important and should be considered importantly in chemotherapy since its administration as combined with cisplatin and sunitinib enhances the VEGF inhibitory effect of cisplatin (Maj et al. 2018), though the effect of the vitamin on VEGF is still cloudy. Opposite the claims of Maj et al. (2018) above, vitamin D (1,25(OH)(2)D(3) is claimed to increase the expression of VEGF which induces the progress of cancer by angiogenesis. (Cardus et al. 2009; Zhong et al. 2014; Jamali et al. 2014). Therefore, the vitamin may be tried in the treatments with cisplatin and sunitinib but the regular vitamin D rich food consumptions which include 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, until its effect on VEGF becomes clear. Allthough Huo et al. (2010) claim the inhibitory effect of arginine (≤0.5 mmoL/L) on VEGF, because of the inducing

effect of nitric oxide which is the end product of arginine (Abe et al. 2013), arginine and arginine rich 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.2016-Release 28; Uhlmann et al. 2001), might be contraindicated with the VEGF inhibitors since they induce VEGF activity and its expression, like vitamin D. The current findings about the effect of folate, folic acid and B vitamins on VEGF via homocysteine (Hcy) are conflicted. According to Aronson and Zhang (2016), Hcy reduces the expression of VEGF factor A and its receptor 2 (VEGFR2) and therefore, reducing homocyteine with folate, folic acid or B vitamins might increase VEGF. Confirmingly, Oosterbaan et al. (2012) and Kim et al. (2011) claim that Hcy inhibits vascular development with a significant reduction of vessel area and altered composition of the vascular beds while reducing VEGF-A, VEGFR-2, ERK1/2 and Akt. On the other hand, Roybal et al. (2004) and Atta et al. (2008) disclaim the findings. Therefore, it may be useful for the patients with cancer to avoid from the foods rich in folate, folic acid and vitamins B, e.g. beef liver, tuna, salmon, chicken breast, banana, ground beef, bulgur, squash, nuts, onion, spinach, turkey meat, tofu, raisins and watermelon, black-eyed peas, asparagus, Mustard greens, green peas, kidney beans, peanuts, crab, orange, yeast, egg, cantaloupe, milk, chicken breast, clams, milk, yogurt, cheese, trout and egg (USDA 2011, 2012), until the cloudy status of 'folate, folic acid and B vitamins and VEGF' association becomes clear. Finally, quercetin is informed to activate and upregulate cancer cells while stimulating of VEGFR-2 and HIF-1α (Jeon et al. 2007; Donnini et al. 2006 and Zhou et al. 2015). Therefore the limitation of the quercetin rich foods; onion, kale, broccoli, lettuce, tomatoes, asparagus, red leaf, lettuce and green pepper may also be useful and recommended during the administrations of the mentioned VEGF and HIF-1α inhibiting drugs.

4

METALLOPROTEINASES AND THEIR ASSOCIATION WITH CANCER

Matrix metalloproteinases (MMPs) are consisted of a multigene family of zinc-dependent collagenous extracellular matrix (ECM) endopeptidases whose activity plays a vital role in invasion of tumor growth and metastasis (Gialeli et al. 2011). Cancer cells disseminate to other tissues and induce metastasis by degrading their surrounding ECM and making a way to the vascular system. They use the special enzymes, 'metalloproteinases', to degrade ECM. High levels of MMPs have often been associated with increased levels of tumor invasion (Deryugina and Quigley 2006). During cancer progress, thrombin and thrombin receptor-activating peptides induce MMP secretion which is paralleled by an increase in the bridges for cell-cell and cell-extracellular matrix (ECM), which are crucial in cancer initiating signaling through cells (Radjabi et al. 2008). After the signal, 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 of which contribute to the dissemination of cancer cells in ECM. Some of the most commonly known MMPs, MMP2 and 9, are capable of cleaving ECM like other MMPs and therefore they are crucial in tumor progression and metastasis (Ala-aho and Kahari 2005). Metalloproteinase enzymes also increase the risk of tumorogenesis since they decompose metalloproteins which make metals free and activated. The chemotherapeutic agents which are currently administered in cancer treatments to inhibit MMP (the agents whose inhibitory effects

on the enzymes were observed by the references in the following paranthesis) are; 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) (Woltowicz-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), 17AAG (Singh et al. 2015), raloxifene (Bellosta et al. 2007), naproxen, 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). On the other hand, soy and soy products reveal a crucial characteristic in cancer nutrition since they contain an important enzyme, TIM-2, and another MMP inhibitor, genistein (40 μM/L/48h on human endometrial cancer cell lines, Ishikawa and HEC-1B) (Liu et al. 2016). On the other hand, the high dose arginine intraperitoneal (i.p) injections (≥200 mg/Kg) inhibit the MMP activity (Hnia et al. 2008). Like soy saponins and high dose arginine administrations, other food bioactive compounds with their inhibitory effects on MMP (the food/plant bioactive compounds whose inhibitory effects on the enzymes were observed by the references in the following paranthesis) are as follows; EGCG (plant source: *Camellia sinensis*, EGCG, 0.1%, directly on MMP-9,13) (Kim-Park et al. 2016), resveratrol and its rich sources (resveratrol, 40 mg/Kg, in the cortical and strial regions of brain in rats after i.p. injection) (Pandey et al. 2015), quercetin and its rich sources (quercetin, 60 μM/36h, in the human hepatocellular carcinoma cell line, HCCLM3) (Lu et al. 2018), apigenin and its rich sources (apigenin, 100 μM/24h, in normal human dermal fibroblasts with UVA-induced cytotoxicity) (Choi et al. 2016), I3C and carbazole (the plant source for both is cruciferous vegetables) (I3C or carbazole, 10 μM/48h, in the breast cancer cell lines; MCF-7

and MDA-MB231) (Ho et al. 2012), turmeron (the oil which is isolated from *Curcuma longa*, turmeric) (turmeron, 20 μM/24h, in the human breast cancer cell line, MDA-MB-231) (Park et al. 2012), β-carotene and its rich sources (β-carotene, 20 μM/48h, in the neuroblastoma cell line, BE(2)C) (Kim et al. 2014), lycopene and its rich sources (lycopene, 10 μM/48h, in HUVECs) (Chen et al. 2012), ascorbic acid and its rich sources (ascorbic acid, 100 μg/mL/96h, in the leukemia cell lines; HuT-102 and C91-PL) (Harakeh et al. 2018), α-tocopherol derivative (2,2,5,7,8-pentamethyl-6-hydroxychromane, PMC) (100 μM/24h, in vascular smooth muscle cells) (Hsieh et al. 2014), kaempferol and its sources (kaempferol, 100 μM724h, in the human renal cell adenocarcinoma cell line, 786-0, and human proximal tubule epithelial cell line, HK-2) (Hung et al. 2017), amygdalin and its sources (amygdalin, 10 mg/Kg/d for 4 weeks intraperitoneal injection in mice and 10 mg/mL/24h in the kidney carcinoma cell lines, Caki-1, KTC-26 and A498) (Lv et al. 2017; Juengel et al. 2016), folic acid and its sources (folic acid, 80 μg/Kg, in spinal cord tissue samples of rat) (Miranpuri et al. 2017; Guo et al. 2006), L-arginine (10 %, 30 g, intra venous (i.v) injection in human subjects and 1000 μmoL/L/24h, in the human colorectal adenocarcinoma cell line, SW480) (Garcia et al. 2016; Yeh et al. 2010), vitamin D and its rich foods (calcitriol, 10 μM/48h, in nasal fibrobilasts) (Wang et al. 2015), sulforaphane and its rich sources (sulforaphane, 10 μM/24h, in the human breast cancer cell line, MCF10DCIS) (Bao et al. 2015) and isoliquiritigenin (a phenolic compound in licorice and the plant source is *Glycyrrhiza uralensi*) (isoliquiritigenin, 20 μM/72h, in articular chondrocytes) (Zhang et al. 2018) (Figure 2). It should be carefully noted that the findings of Choi et al. (2016) about the effect of apigenin on MMP also indicate to a likely potential of apigenin for the protection from cancer risk due to Ultraviolet radiation. The findings of Guo et al. (2006) may be crucial since they inform the triggering effect of folate deficiency (50-1000 μM/L/48, in rat vascular smoothe muscle cells) on MMP. Based on their synergism to inhibit the kinases, these food/plant bioactive compounds might have been beneficial if they are consumed during the chemotherapy which administer the mentioned MMP inhibitors. When the regulation of 'fat intake' and 'the type of fat' during the administrations of MMP inhibitors are concerned, the

findings clearly indicate to the benefits of Omega 3 and 6 fatty acids. Alpha-linolenic acid or linoleic acid (70 μM/24h, directly on MMP-2 and MMP-9 progelatinases) (Nicolai et al. 2017) treatment clearly indicates the inhibitory effects of the Omega 3 and Omega 6 fatty acids on MMP. Confirmingly, Omega-3 fatty acid supplementation (30 μg/mL/8h, in bovin chondrocytes) (Zainal et al. 2009) and the supplementations of EPA and DHA (3g/d for 6 months) in proportion of 0.9-1.5 (Derosa et al. 2009) has the similar effect. The findings of Lu et al. (2018) may be crucial since the supplementation of Omega-6 fatty acids which are well known with its inflammatory leukotrients and prostaglandin E2 (0.5 g/Kg/7d, in rat) have the inhibitory effect on the expressions of MMP-2 and MMP-9, while these fatty acids increase the expression levels of the important antioxidant genes; Gpx which converts harmful hydrogen peroxide to water and hydrogen), GHS (glutathione) and SOD (the enzyme which converts harmful superoxide radicals to molecular oxygen and hydrogen peroxide). The findings clearly indicate to the significantly important inhibitory potential of Omega fatty acids no matter what their origin is. Even the inflammatory effects of Omega 6 fatty acids should occasionally be evaluated as a response and defence to a pathologic incident rather than 'being inflammatory'. Finally, the association of sulforaphane with MMP is significantly different since the flavonoid has its inhibitory effect on MMP via the over-activation of Nrf2. Nrf2 works as in close relation with phase 1 and 2 enzymes. Phase 1 enzymes regulate 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, the products from phase 1 reactions are often rendered more reactive than the original toxins which make them more destructive than they once were. Additionally, phase I reactions are not sufficient enough to make toxins water-soluble to complete the excretion. So, both of phase I and II enzymes increase the solubility of these toxic compounds and reduce their toxicity. The production of most phase II enzymes is controlled by the protein, Nrf2, the master regulator of antioxidant response. Sulforaphane suppresses ultraviolet A-induced MMP-1 and AP-1 (the transcription factor activator protein 1, which binds and activate

oncogenic proteins) in UVA-irradiated HaCaT (the human aneuploid immortal keratinocyte cell line) by inducing the activity of Nrf2, while this induction inhibits MAPKs (Chaiprasongsuk et al. 2017). The best known MAPKs are ERK1/2, JNK 1, 3, p38 (α, β, ϒ, and δ) and ERK_5 (which act importantly in the regulation of nucleosome and gene expression, mRNA stability, cell proliferation and survival) (Cargnello and Roux 2011). On the other hand, 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). Moreover, the MAPKs regulate the activity and expression of the inflammatory proteins which may function as potent cancer promoters. The inhibition of p38 and JNK by Nrf2 which is induced by sulforaphane, directly inhibits cell proliferation but also activates caspase-3 degrading ADP-ribose polymerase protein, (the protein to repair DNA) and leads to apoptosis (Avisetti et al. 2014) (Figure 2). All these details point out the formation of apoptosis which is induced by Nrf2, followed by the inhibitory effect of sulforaphane on MMP, AP-1, MAPK, VEGF, TNF-α, NF-kβ and induction on caspase-3 (Figure 2).

5

THE DESIGN OF THE DIET DURING THE CHEMOTHERAPY WHICH ADMINISTERS TNF INHIBITORS

TNF-alpha (TNF-α), a member of the TNF/TNFR cytokine superfamily, is involved in the maintenance and homeostasis of the immune system, inflammation and host defence. But, it is also involved in pathologic processes like the progress of malign tumors. The anti-apoptotic and cancerogenic side of the gene may be due to its triggering effect on the expression of CXCR4 (the chemokine, a small cytokine which enhances cell adhesion, survival, proliferation and gene transcription) (Zhao et al. 2010), CCL8 (a chemokine which acts in cancer cell dissemination) (Secchiero et al. 2005), VEGF (Jing et al. 2011), MMP (Tsai et al. 2014), CCL11 (an eosinophil protein which induces chemotaxis of eosinophiles during inflammation) and finally CRP (the protein which is produced by liver in inflammation) (Mikirova et al. 2012; Li et al. 2010). The bad prognose in the further stages of cancer due to the up-regulation of TNF-α in cancer cells has made the gene an important target in cancer therapy. The TNF-α inhibitors have gained important status and application field in chemotherapy. The TNF-α inhibitors (the agents whose inhibitory effects on the gene were observed by the references in the following paranthesis) which are currently being administered are as follows; 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), quinolactacin A (Sasaki et al. 2006) and quinolactacin B (Tatsuta et al. 2001). On the other hand, the food bioactive compounds (the bioactive compounds whose inhibitory effects on the gene were observed by the references in the following paranthesis) (and in all of the next part of the review, the parentheses which include the author and date are the studies which confirmed or determined the anticancerogenic effect of the drug or bioactive compound, like it was alsomentioned in 'important part'- page iii) are as follows; sulforaphane and its rich sources (30 μg/mL/24h, in the mouse endothnelial cell line, bEnd.3) (Wu et al. 2016), kaempferol (5 mg/Kg in rat and 80 μM/24h, in synoviocytes) (Pan et al. 2018; Guo and Feng 2017), myricetin and its rich sources (5 mg/Kg in rat or 25 μM/24h, in the human aneuploid immortal keratinocyte cell line, HaCaT, fisetin (sources e.g., strawberry, apple, persimmon, grape, onion and cucumber) (5 mg/Kg in rat or 80 μM724h, in the human airway epithelial cell lines; NCL-H292 and HEK293T) (Guo and Feng 2017; Arai et al. 2000; Lee and Lee 2016; Lee et al. 2018), genistein and its sources (genistein, 40 μM/24h, in the synoviocyte cell line, MH7-A cells) (Li et al. 2014), amygdalin and its rich sources (amygdalin, 10 mg/mL/24h, in the renal cell carcinoma cell lines, Caki-1, KTC-2b and A498) (Juengel et al. 2016), resveratrol and its rich sources (resveratrol, 50 μM/24h, in the adipocyte cell line, 3T3-L1) (Zhu et al. 2008), folic acid and its rich sources (folic acid, 11.3 μM/24 h, directly in THP-1 macrohages), choline and its rich sources (e.g. egg, liver) (105 μM choline chloride/24h, directly in THP-1 macrohages), vitamin B_{12} (18.5 nM/24 h, directly in THP-1 macrohages) (Samblas et al. 2018), apigenin and its rich sources (apigenin, 20 μM/24h, in the airway epithelial cell line, NCl-H292) (Seo et al. 2014), quercetin and its rich sources (quercetin, 20 μM748h, in myotubes, skeletal muscle fibers) (Kim et al. 2018), alpha toocopherol and its rich sources (alpha toocopherol, 1200 IU/d for 3 months, in human subjects and 80 μM/24h, in the bovine kidney epithelial cell line, MDBK and 1200 IU/d for 3 months in human subjects) (Li et al. 2012; Devaraj and Jialal 2005), EGCG and its sources (EGCG, 50μM/24h, in human aortic endothelial cells, HAECs) (Yang et

al. 2016) and ascorbic acid and its sorces (ascorbic acid, 200 μg/mL/24h, in nucleus pulposus cells) (Dai et al. 2015). On the other hand, not all food bioactive compounds are in synergism with TNF inhibitors. I3C and its rich sources (I3C, 100 μM/24h, in the immortalized rat liver stellate cell line, HSC-T6 and 50 μM/48h, in Jurkat cells) (Li et al. 2017) might be contraindicated since I3C activates the expression of TNF-α. Similarly, vitamin D (1α,25-dihydroxyvitamin D_3 (1α,25$(OH)_2D_3$, calcitriol) should better be avoided during the administrations of TNF-α inhibitors, since the gene might be activated by the vitamin (10 nM/24h, in the human prostate cancer cell lines, LNCaP and PC-3) (Golovko et al. 2005). Also, the vitamin and the gene induce each other, like in the increase of the expression and the activity of the vitamin by the gene (Ziv et al. 2016). The findings of Kim et al. (2018) about the effect of quercetin on TNF-α are particularly important. The flavonoid suppresses the expression of TNF-α and induces Nrf2, both of which may contribute to a better prognose especially during and after the administrations of TNF-α and NF-kB inhibitors. On the other hand, it also induces the expression of HO-1 which may increase the resistance of cancer cells against anaerobic conditions during chemotherapy and thus, might have been contraindicated during the treatments which administer HO-1 inhibitors. The status of L-arginine from the point of its effect on TNF-α and cancer seems exclusive and should always be taken into consideration in an anti-cancer diet. The supplementation of L-arginine as a nitric oxide precursor elevates nitrotyrosine (a fingerprint of peroxynitrite which is a significant indicator of nitrative stress) and enhances TNF-induced increase of nitrotyrosine production which exacerbates TNF-mediated cell apoptosis (Xia et al. 2010). Therefore, L-arginine rich foods might be contraindicated during the administration of TNF inhibitors. The apoptotic effect of EGCG has a significant role and status, because of a new target in chemotherapy, ADAM10, which plays an important role as in a close relation with the flavonoid. ADAM10, the transmembrane metalloproteinase, sheds a range of cell surface proteins including ligands and receptors of the Notch (the anti-apoptotic signaling which is produced by the transmembrane proteins, the Notch receptors, although the signaling may sometimes be tumor suppressive depending on the type of cancer) (Aster et al. 2017), Eph (ephrin, a

superfamily of tyrosine kinases, whose overexpression and deregulation is often involved in tumorigenesis and angiogenesis) (Lodola et al. 2017) and ErbB (the receptor family of tyrosine kinases, which includes EGF, an important contributer to tumor progress). On the other hand, EGCG causes ADAM10-dependent ectodomain shedding of TNF receptor 1 and inhibits TNF-α-induced endothelin-1 (a small anti-apoptotic bioactive peptide). As a result, the isoflavonoid attenuates the effects of TNF-α (Yang et al. 2016). EGCG is a clear example as a food bioactive compound which has a wide range of anti-cancerogenic effects from its effect on TNF-α to ADAM10, Errb, EpH and Notch. Finally, ascorbic acid's importance during the TNF inhibition is concurrently with its triggering effect on the expression of extracellular matrix. The vitamin inhibits TNF-α, but delays the apoptosis which is induced by TNF-α while it increases the expression of extracellular matrix (Dai et al. 2015). Therefore, consumption of too much ascorbic acid rich foods, e.g. citrus fruits, might have been contraindicated with the TNF-α inhibitors, in addition to the risk of their rich fructose contents.

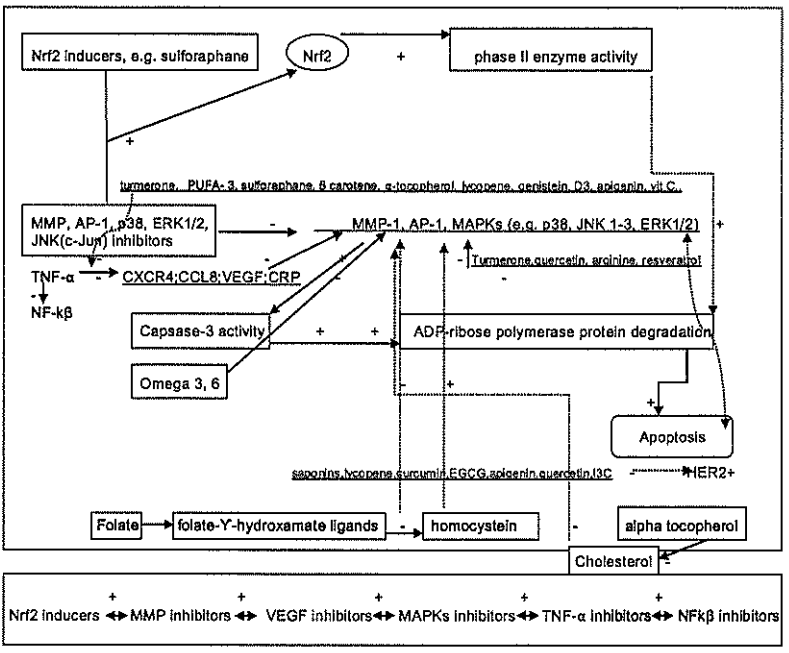


Figure 2. The close interrelation of Nrf2, MMP, VEGF, MAPKs to induce apoptosis.

6

NRF2, THE GENE WITH ITS DUAL EFFECT AND ASSOCIATION WITH CHEMOTHERAPEUTIC AGENTS/ FOOD BIOACTIVE COMPOUNDS

The Nrf2 signaling pathway consists of three main components as Keap 1, Nrf2, and ARE. These components function respectively as the sensor, controller and responder. Nrf2 is essential for homeostasis and protection against oxidative stress while it suppresses tumor progress by reducing the oxidative stress but the constant activation of Nrf2 may cause to form various cancers and resistance to chemo-and radiotherapy. Although the Kelch-like ECH-associated protein 1/nuclear factor erythroid-derived 2-like 2 (KEAP1-NFF2) system is a defense against oxidative stress, its persistent activation in cancer cells may often develop 'Nrf2 addiction' of cancer cells and malignant phenotypes with poor prognose (Kitamura and Motohashi 2018). One of the greatest dilammas and drawbacks in anticancer treatments is the dual effects of many cancerogenic proteins, genes and signaling, including Nrf2. The gene has traditionally been considered as a tumor suppressor because of its cellular defense against intrinsic and extrinsic cancerogenic substances including xenobiotics (chemicals which are detoxified in liver and not produced in organism) and oxidative stress. In contrast, the hyperactivation of the gene creates an environment which does not only favor healthy cells by protecting them from ROS, radiotherapy and chemotherapeutic agents, but also cancer cells. That the Nrf2-deficient mice are more sensitive to cancerogenic substances and Nrf2 loss has

been related to enhanced metastasis, is also a clear example of the dual action of the gene. For all these reasons, either the activation or inhibition of the gene has been administered in anticancer treatments. The increase in the genes, Cul3 (Cullin3) and Keap1, is often associated with the decrease in Nrf2, while Keap1 inhibits the activity of Nrf2 by binding it (Taguchi and Yamamoto 2017) and the overexpression of Cul3 depletes Nrf2 which increases the sensitivity of healthy cells to cancerogenic substances as well as chemotherapy (Loignon et al. 2009). As a result, the activation of Nrf2 and inactivation of Cul3 and Keap1 or opposite, the inhibition of Nrf2 and activation of Cul3 and Keap1, has become one of the novel approaches in anticancer treatments. It is not difficult to expect the side effects of both treatments since they weaken not only cancerous cells but also the healthy ones. Because the treatments are completely opposite to each other, naturally the interactions of the foods and drugs during each treatment should be different. If the treatment administers Nrf2 activating drugs, like verapamil (a drug to relief hypertension) which activates Nrf2 through the induction of p62, a multidomain protein with autophagy-dependent apoptotic activity as dependent autophagic Keap1 degradation (Lee et al. 2017; Islam et al. 2018), then sulforaphane rich foods may be advised. Because, it is the most effective isoflavanoid in the activation of Nrf2. The isoflavonoid (2.5μM/5d, in the prostate cancer cell line, TRAMP C1) causes demethylation of CpG sites (the regions of DNA where a cytosine nucleotide is followed by a guanine nucleotide in a linear sequence) which results in Nrf2 activation (Zhang et al. 2013). On the other hand, the term 'CD value' is often used to determine the Nrf2 activating potential of food bioactive compounds. The value is the concentration which is required to double NQO1 (quinine oxidoreductase, an enzyme that catalyzes the reduction of quinine substrates in chemotherapeutic or anti-chemotherapeutic effect) activity in murine hepatoma cells. It is used to compare the potential in vivo nutrigenomic effects of an ingestible bioactive compound (Fahey et al. 2005; Houghton et al. 2016). When the CV values of the food bioactive compounds are compared, sulforaphane appears as the first Nrf2 inducer, with 0.2 μM. The CV values of other bioactive compounds in Nrf2/NQO1 activation are as follows; andrographolides, a C20 labdane diterpenoid isolated from

Andrographis paniculata, with an anti-inflammatory, antiviral, antithrombotic, hypotensive and antiatherosclerotic effect (1.43 μM), quercetin (2.50 μM), β-carotene (7.2 μM), lutein (17 μM), resveratrol (21 μM), I3C (50 μM), chlorophyll (250 μM), alpha-cryptoxhanthin (1.8 mM), zeaxanthin (2.2 mM), curcumin (2.7 μM), silymarin (3.6 μM), genistein (16.2 μM), EGCG (>50 μM) and ascorbic acid (>50 μM) (Jeffery and Stewart 2004; Fahey and Kensler 2007; Yang and Liu 2009; Gerhauser et al. 2003 and Houghton et al. 2016). Additionally, EGCG (50 μM/1h, in MDCK renal tubular cells) activate the gene (Kanlaya et al. 2016). So, the anticancerogenic diet during the treatments which administer the Nrf2 activators should be consisted of beta carotene rich foods; carrot, sweet potato, pumpkin, broccoli, collard greens, red palm oil, orange fruits and leafy green vegetables (USDA 2012), lutein rich foods; egg yolk and corn (as the most richest ones), kiwi, red seedless grape, pumpkin, spinach, orange pepper, yellow squash, cucumber, pea, green pepper, celery, Brussels sprouts, scallions, orange, broccoli, apple and mango (Sommerburg et al. 1998), I3C rich foods; cruciferous vegetables like Brussels sprouts and Cabbage family (Fujioka et al. 2016), andrographolide (*Andrographis paniculata*), chlorophyll; Chinese kale: *Brassica oleracea var. alboglabra Bailey*, Chinese flowering cabbage: *Brassica ropa L. var. parachinensis*, spinach, water spinach, cassava leaf, green leaf, lettuce, basil, sword-leaf lettuce: *Lactuca sativa L. var.augustana*, head cabbage: *Brassica oleracea L. var capitata* (Limantara et al. 2015), alpha cryptoxhantin rich foods; carrot, tomato and papaya (Burri 2014), zeaxanthin rich foods; green bean, broccoli, collard, parsley, spinach, orange, mandarine, plum (red), papaya, mango, orange and peach (Humphries and Khachik 2003), curcumin rich foods; turmeric and curry (Tayyem et al. 2006), silymarin; *Silybum marianum* (milk thistle) (Surai 2015) and genistein rich foods; currants, raisins, satsumas, Brazil nut, chestnut, coconut, bazelnut, sesame seeds. The protein source in the treatments by Nrf2 inducers should be selected as egg-derived peptides, since the peptides, DKK and DDW, can inhibit the Keap1-Nrf2 interaction (Li et al. 2017) and induce Nrf2. When the preference of fat in the treatments is considered, Omega 3 PUFAs (100 μM DHA or EPA/24h on the necrotic cells, astrocytes) were claimed to induce the gene (Zgorzynska et al. 2017) and therefore, their involvement

in anti-cancer diet might have been useful during the treatments with the Nrf2 inducers. On the other hand, if the approach is the administration of Nrf2 inhibitors, e.g., IM3829 (4-(2-cyclohexylethoxy) aniline), ARE expression modulator 1 (AEM1), isoniazid (Zhu et al. 2016), ML385, a probe molecule that binds to Nrf2 (Singh et al. 2016), CPUY192018 (Lu et al. 2016), 1,4-diaminonaphthalene compounds (Zhuang et al. 2017), ethionamide (ETH) (an antibiotic to treat tuberculosis with bacteriostatic and bactericidal effect) (Peng et al. 2016), 4-methoxyxhalcone (as synergic with cisplatin!) (Lim et al. 2013), IM3829 (4-(2-Cyclohexylethoxy aniline) (lee et al. 2012), brusatol (very effective particularly in Hepa-1c1c7 cells!) (Olayanju et al. 2015), metformin (1,1-dimethylbiguanide hydrochloride, an oral hypoglycemic agent) (Do et al. 2013), doxorubicin and etoposide (Peng et al. 2016), then a diet rich in the following foor/ plant bioactive compounds with their Nrf2 inhibiting effects might have been useful by creating a synergism via the inhibition of the gene. These food/plant bioactive compounds are; wagonin (40 μM/4h, in the human myelogenous leukemia cell lline, K562) (5, 7-dihiydroxy-8-methoxyflavone), a flavonoid in the root of *Scutellaria baicalensis* Georgi (Xu et al. 2017), luteolin (80 mg/Kg/21d, in non small cell lung cancer cells, NSCLC), a flavonoid in plants, and vegetables e.g. dried oregano berries, green or yellow chilli peppers, radicchio (Chian et al. 2014), chrysin (60 μM/72h, in the hepatocellular carcinoma cell line, HCC, and 20 μM/48h, in the hepatocellular carcinoma cell line, BEL-7402) (Xu et al. 2017; Gao et al. 2013), 3, 4, 5, 5, 7-pentamethoxyflavone (PMF) (in the plants of *Rutaceae* family such as *Murraya paniculata* and *Neoraputia magnifica* (50 μM/1h, in the human lung carcinoma cell line, A549) (Hou et al. 2015), quassinoid (a triterpene lactone) (40 nM/24h, in the human non-smaill-cell lung cancer cells) (Fiaschetti et al. 2011), trigonelline (0.5 mM/16h, in the colon cancer cell line, Colo357) (Arlt et al. 2013), cryptotanshinone (CTS) (200 μM) (a quinoid diterpene isolated from the root of the Asian medicinal plant *Salvia miotiorrhiza* bunge and a potential sensitizer to revert cisplatin resistance of human lung carcinoma A549 cells by inhibiting Nrf2!) (Xia et al. 2015), chestnut leaf extract (*Castanea crenata*) (decreases chemoresistance to paclitaxel by inhibiting Nrf2!) (50 μM/mL, in the human breast cancer cell line, MCF-7) (Woo et al. 2017) and retinoic acid (1 μM/24h, in the

breast cancer cell line, MCF-7) (Wang et al. 2007). More important is that luteolin increases the sensitivity of cancer cells to oxiplatin, bleomycin, doxorubicin and actinomycin D, while apigenin and chrysin increase the sensitivity of cancer cells to doxorubicin and quassinoid. Brusatol from the plant, *Brucea javanica* increases the sensitivity of cancer cells to cisplatin, carboplatin, 5-fluorouracil, etoposide and paclitaxel and finally, trigonelline increases the sensitivity to etoposide (No et al. 2014). All these food/plant origin bioactive compounds make the mentioned improvements in the effect of chemotherapy by inhibiting the gene. Nevertheless, the status of ascorbic acid on the gene still needs to be highlighted since there are only two studies which have completely opposite findings. Tarumoto et al. (2004) inform the Nrf2 inhibitory effect of ascorbic acid (0.125 mM/6h, in chronic myelogenous leukemia cells, KCL22/SR), while Mostafavi et al. (2017) claim the inducing effect of the vitamin (1000 μM/24h, in the breast cancer cell lines; MDA-MB 231, MDA-MB 468, MCF-7 and human lung cancer cell line, A549) on the gene. Therefore, it may be safe and cautious to limit the ascorbic acid rich foods like; strawberry, kiwi, grapefruit, persimmon, apple, mandarin, mango, pear and pineapple (Szeto et al. 2002), until the effect of the vitamin on Nrf2 becomes clear. Similarly, apigenin (50 μM/5d, in JB-6 mouse epidermal cells) induces the gene according to the findings of Paredes-Gonzalez et al. (2014), while the opposite has been claimed by Gao et al. (2013) (20 μM/24h, in the hepatocellular carcinoma cell line, BEL-7402). Therefore, the flavonoid should better be avoided or limited until its effect on the gene becomes clear. No need to mention that the Nrf2 inducing food/plant bioactive compounds might be contraindicated with the drugs and food-bioactive compounds which inhibit the gene.

7

MDR1 AND ITS ASSOCIATION WITH NUTRITION

MDR1 gene is expressed in tumor cells and also in normal tissues, such as intestine, liver, kidney, blood-brain barrier, spinal cord and plasenta. Currently, there is significantly huge amount of data that indicates to the limitation in intestinal absorption and brain access of many drugs by the expression of the gene. In fact, the gene may be considered as one of the integral parts of defence system since it prevents drug entry into the central nervous system. But, MDR1, the member of P-glycoprotein (P-gp) gene family, also interferes with drug bioavailability and disposition, including the absorption, distribution, metabolization, excretion and thus affect the pharmacokinetic and pharmacodynamic of drugs including chemotherapeutic agents, particularly; paclitaxel, doxorubicin, daunorubicin, vinblastine, vincristine, actinomycin D, docetaxel, etoposide, imatinib and teniposide (Linardi and Natalini 2006). The promotive effect of Her2 on MDR1 and MMP via MDR1 evoked by P-gp, should never be neglected, particulary in MDR breast cancer (Jin et al. 2016). Currently, the current stage has come to a point in which some of the food bioactive compounds could be combined with the therapeutic agent to be able to enhance its bioavailability via the synergism of the food bioactive compound with the chemotherapeutic agent to inhibit the gene. Accordingly, folic acid (400 μg/14 week supplementation) (Obermann-Borst et al. 2011), sulforaphane (20 μM/24h, in the lung cancer cell line, A549 and A549/T) ((Ji et al. 2017), ascorbic acid (500 μM/100 min., in MDCK-MDR1, the cell line which

originates from transfection of Madin Darby canine kidney, MDCK cells with the MDR1 gene) (Luo et al. 2008), I3C (5 mg/Kg intraperitoneal administration for 3 consecutive days, in mice) (Arora and Shukla 2003), vitamin D (10-9 mg/mL/48h, in the human chronic myeloid leukemia multi-drug-resistant cell line, K562/ADR) (Yan and Nuriding 2014), kaempferol (256 μg/mL/48h, in *Candida albicans*) (Shao et al. 2016), apigenin (100 μM/72h, in the breast cancer cell line, MCF-7/ADR) (Seo et al. 2017), sesquiterpene lactone 6-O-angeloylplenolin (1.4 μM/24h, in the colon carcinoma cell line, HCT-8) (Li et al. 2018), terpenoid various terpenoids, e.g., safranal, cucurbitacin E, lupeol, limonin and nomillin (1 mM/1h, in the pig kidney cell line, LLC-GA5-COL150 and colon cancer cell line, Caco-2) (Yoshida et al. 2006), capsaicin (50 μM/24h, in the colon cancer cell lines, Caco-2, and HCT116), piperine (65 μM/24h, in the colon cancer cell lines, Caco-2, and HCT116, an important note is that either capsaicin or piperine can overcome MDR1 resistance in cancer cells to doxorubicin) (Li et al. 2018) and curcumin (10 μM/72h, in the retinoblastoma cell line, Y79-MDR1) (Sreenivasan et al. 2013) inhibits the overexpression of the gene. It may be crucial and useful to follow a nutrition rich in these food bioactive compounds during the administrations of the chemotherapeutics which target the gene, e.g. elacridar (Chen et al. 2017), 8-prenylnaringenin (Wesolowska et al. 2010), celecoxib (Roy et al. 2009), voruciclib (Gupta et al. 2018), acridon carboxamide derivative, GG918 (Wallstab et al. 1999), the first generation chemotherapeutics in plant origin; verapamil, nifedipin, cyclosporine A, ibuprofen, reserpine, tamoxifen, amidarone, the second generation chemotherapeutics in plant origin; valspodar, dexverapamil, MM36, cinchonine and quinine homodimer, MM36, cinchonine and quinine homodimer Q2 and the third-generation chemotherapeutics in plant origin; tariquidar, zoruquidar, PGP4009 (Yu et al. 2016), PSC-833 (van der Holt at al. 2005), MK-571 (Fukuda et al. 2010), reversin 121 and reversin 205 (Sharom et al. 1999) and dexniguldipine-HCL (Hofmann et al. 1994). The chemotherapeutics and the food bioactive compounds in the combined use might have formed a synergy to inhibit MDR1 and P-gP (P-glycoprotein, the transporter membrane which is comprised of 1280 amino acids and an energy-dependent drug efflux pump which is encoded by the human MDR1 gene). This synergism may

increase the bioavailability of the chemotherapeutics and enhance their anticancerogenic potential. On the other hand, the effect of resveratrol on the gene is still not clear and needs further studies to be highlighted. The treatment of lymphoblastic leukemia cells with the flavonoid (50 μmol/l/48h) is claimed to increase the expression of the gene in only one patient while it did not have any effect on other patients (poor Feyzi et al. 2015). However, the same flavonoid down-regulated the expression of the gene in the study of Zadi Heydarabad et al. (2018) (100 μM/48h, in the acute lymphoblastic leukemia cell line, CCRF-CEM). Like resveratrol, the association of quercetin with the gene is still not obvious because of the conflicted claims. While Kioka et al. (1992) claims that quercetin (100 μM/4d, in the human hepatocarcinoma cell line, HepG2) inhibits the expression of the gene, Chae et al. (2016) (0.1 μM/1d, in the colon cancer cell line, Caco-2) claims the opposite. The reason for the opposite findings may be due to the the parameter of 'dose' that, the inhibitory effect was observed with a very high dose (100 μM) and longer treatment period (4d) in the study of Kioka et al. (1992) when compared with the much lower dose (0.1 μM) and shorter treatment period (1d) in the study of Chae et al. (2016) who claim the inducing effect of the flavonoid on the gene. The effect of vitamin A on the gene is strongly dependent on the form. Lycopene, lutein, antheraxanthin and rhodamine (1.0 μg/mL/24h, in mouse T-cell lymphoma cells, L5178Y) moderately down-regulate the expression while alfa and beta carotene have no effect (Molnar et al. 2004). It may be vitally important to consider the inducing effect of genistein (10 μM/48h, in the hepatocellular cancer cell line, HepG2) on the gene (Rigalli et al. 2015). The flavonoid also increases the sensitivity of cancer cells to sorafenib cytotoxicity. There is still no study about the effect of amygdalin on the gene although it has got significant anticancerogenic potential besides its toxicity. α-tocopherol (10 mg/100g body weight, daily subcutaneous injection up to 18 days, in rat) causes increases in overexpression of the gene after 6th day of the supplementation and the increase reaches its peak point at 15th day (Mustacich et al. 2006). Arginine was reported to increase the overexpression of the gene via the methylation process by arginine methyltransferase which serves to the DNA repair and mRNA slicing of cancer cells (Li et al. 2016).

On the other hand, the methylation by arginine methyltransferase has only recently been linked to carcinogenesis though it has often been associated with various cancers (Yang and Bedford 2012). So, the rich nutrition in arginine should be limited during chemotherapy which administers the MDR1 inhibitors, but it should never be neglected in other periods since it is an indispensible and essential nutrient for the immune system.

7.a. The effect of EGCG on the MDR1 gene: A clear example that indicates to a no-way-out for now in anticancer nutrition and chemotherapy while continuing to ride on the same circle!

The expression of MDR1 in cisplatin-resistant CAL27 (CAR) cells could be inhibited by EGCG (100 μM/24h as combined with the administration of cisplatin, 100 μM) by activating Akt/STAT3 (Yuan et al. 2017). The findings are particularly important since they clearly reveal the ability of EGCG to decrease the cisplatin resistance in cancer cells by inducing the pathway of Akt/STAT3, a pathway which often appears as cancerogenic. Unfortunately, almost all pathways, proteins and enzymes which have crucial roles in the progress of cancer, are also essential, indispensable and beneficial for healthy cells and especially immune cells, like in the example of Akt and STAT3 signalings. These signalings initiate the proliferation and growth of the cells in the immune system as well as the proliferation and growth of cancer cells. Accordingly, the inhibitory effect of the flavonoid on MDR1 by stimulating cancerogenic signalings like Akt and STAT3, may trigger the growth of the cancer cells while decreasing their resistance to a chemotherapeutic agent. Dual interactions, like the inhibition of a cancerogenic protein/signaling/pathway by inhibiting these proteins, signalings or pathways to form apoptosis or the over-activation of a cancerogenic protein/signaling/pathway by activating these proteins, signalings or pathways to maintain apoptosis, all, are the barriers to make a 'no-way-out' to the current chemotherapies and nutrition. As long as these proteins, pathways, and signalings have dual attributes, 'being essential for not only cancer cells but also healthy ones', the barriers will continue to be exist and we will continue to go on the same circle by killing cancer cells while killing the healthy ones as well.

8

THE DILEMMA OF NITRIC OXIDE (NO), ARGININE AND GLUTAMINE IN CANCER NUTRITION, THE POTENTIAL ROLE OF ARGININE AND GLUTAMINE ON MTOR, NF-KB, COX-2, PI3K, VEGF, HER2, MMP, AND HO-1 INHIBITIONS DURING CHEMOTHERAPY

Nitric Oxide (NO), the free diatomic molecule which is formed from nitrogen in the guanidine of L-arginine, under the catalytic action of the Nitric Oxide Synthase (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 of cysteines in caspases and other related proteins. The induction on S-nitrosylation leads to apoptosis as a result of the caspase activation (Wang and Marsden 1995). But, like in many other cancerogenic pathways, this phenomen is dual since the S-nitrosothiols may also lead to the oxidation of thiol proteins which may activate the cell survival (Mannick et al. 2001; Rössig et al. 1999). So, the first dilemma about the carcinogenic status of arginine and NO appears at this point, and leaves the question behind; 'what may be the reason for the dual effect of the S-nitrosylation, which is sometimes apoptotic and some other times, anti-apoptotic?. The two factors which may turn arginine and NO from anticancerogenic status into cancerogenic, might be the 'dose' and 'time of exposure'. The reason for the cancerogenic effect of arginin/NO might have been the

inflammation which is caused by the long-term exposure to NO, like in the increase of NO which causes colorectal carcinoma progress during ulcerative colitis. The close relation of NO (NO_2, 100-300 μM) with chronic inflammation and NO's contributing effect to the productions of inflammatory cytokines, e.g. IL-8, are claimed by Seo et al. (2009) and Corriveau et al. (1998). The evaluation of the cancerogenic or anticancerogenic potential of NO and arginine and their relation with IL-8 expression closely depend on the factors, 'dose (amount)' and 'time of exposure'. In both studies of Seo et al. (2009) and Corriveau et al. (1998) which claim that NO/arginine are cancerogenic, the NO doses are very lower, 100 and 300 μM, when compared with, 1000 and 2000 μM, the doses which are claimed as strongly anti-proliferative and inhibitory on IL-8, IL-10, IL-6 and TNF-α, by Ridnour et al. (2005) and Lecleire et al. (2008). Some studies prefer to administer very low doses which induce proliferation and inflammatory cytokine production and some others use very high NO doses, e.g.≥ 400 μM, which cause apoptosis and anti-inflammatory effects. Another study which confirms the importance of 'dose' 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 anti-cancerogenic and anti-inflammatory effects of NO including the inhibition on the cytokines like IL-8, when the concentrations are 500 or 1000 μM. Accordingly, the following IL-8 inhibitors; reparixin (Leitner 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) and honokiol (Wang et al. 2015), might have had stronger anticancerogenic effect with a diet which is rich in arginin. Such a diet includes turkey breast, beef, ground meat, lupin, soybean, nuts, seeds, egg white, peanut, mollusk, chickpea, soy flour, sesame seed, lentil, beans, chicken meat, pork meat

and genipin (Gardenia fruit) (Totusek et al. 2011). The higher arginine/ NO concentrations (≥400 μM) in this diet does not only inhibit IL-8, but also the activity and expression of the teratogenic enzyme, Hem oxygenase-1 (HO-1), the 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. The biologically active products which are 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). On the other hand, the association of (HO)-1 with malignancies and the resistance to chemo and radiotherapy due to HO-1, have often been claimed by various studies (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 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 have been regarded as a cellular response to inflammatory response and oxidative injury. Here, the crucial problem and risk are the teratogenic character of the HO-1 metabolites, no matter how they may be regarded as a response to inflammation and oxidative injury. Considering the potential of the teratogenic potential of the HO-1 metabolites, the chemotherapeutic substances which target (HO)-1 inhibition (with their authors who determined their HO-1 inhibitory effects with the studies in the following paranthesis) are; 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 (Sorrenti 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) and OB-24 ([2-(4-bromophenyl) ethyl]-2-2[1H-imidazol-1-yl)methyl]-1,3-dioxolone hydrochloride) (Alaoui-Jamali et al. 2009). On the other hand, only the three food bioactive compounds with the current knowledge, B_6 (35 mg/Kg supplementation in rat for 22 weeks) (Kayashima et al. 2011), ascorbic acid (10 μM/6h, in the murine liver hepatoma cell line, Hepa 1c1c7) (Elbekai et al. 2007) and resveratrol (50 μM/24h, in the adenocarcinoma cell line, A549) (Liu et al. 2010) were observed to down-regulate the expression of HO-1, while no effect was observed for any form of tocopherol (0.3 % α, β, Yor δ toocopherol containing diet for 55 weeks in Her2+ breast cancer cells of mice) (Smolarek et al. 2012). Therefore, if the treatment administers HO-1 inhibitor or a chemotherapeutic agent with the same effect, the diet should be rich in resveratrol, ascorbic acid and B_6. But, most of the other compounds, e.g. EGCG (75 μM/72h, in the human epidermal keratinocyte cell line, HaCaT) (Zhu et al. 2014), quercetin (0.05 % (w/w) quercetin containing diet supplementation for 9 weeks in mice, in the murine myoblast cell line, C2C12), (Kim et al. 2018), kaempferol (10 μg/mL/24h in THP-1-derived macrophages) (Li et al. 2012), chrysin, apigenin and luteolin (25 μM/24h each, in rat hepatocytes (Huang et al. 2013) upregulate the expression of the enzyme. Therefore, the foods which are rich in these food bioactive compounds should be avoided or limited during the treatments which target the inhibition of the enzyme. It should be noted that the following HO-1 inducing food/plant bioactive compounds; 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, e.g. 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; Booth et al. 2006), sulforaphane and sulforaphane rich foods, e.g. white cabbage, Brussel sprouts, radish, mustard, cauliflower, turnip and Chinese kale 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 porl meat and genipin (Gardenia fruit) (Totusek et al. 2011), the foods most of which also contain plant lignans that produce enterolactone (Keum et al. 2006), should be avoided or limited because of their inducing effect on the enzyme if the treatment admininters HO-1 inhibitor. According to the current data about the dual action of NO/arginine which is totally dose dependent, the total concentrations of NO/arginine should never be kept below 400μM to be able to have an apoptotic effect while less concentrations may cause anti-apoptotic effects. High dose NO/arginine approach may also act as apoptotic via the inhibition of COX-2. Confirmingly, L-argine (≥ 440 μM) inhibits tumor cell migration as ≥ 14.2 % in various cancers while decreasing COX-2 levels (Park et al. 2003). Therefore, ≥400 μM arginine 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.

8.a. Could it be a reasonable solution to limit arginin/ NO and/or glutamine in the anticancer diet?

In spite of the important findings about the low dose arginine/NO with its anti-apoptotic effect and high dose arginine/NO with its apoptotic effect, the claims about the arginine's triggering effect on tumor growth still continues to gain a wide acceptance. 33 and 132 mg/L L-arginine blood concentrations as the 2 fold and 8 fold of normal L-arginine blood concentrations decrease the secretion of IFN-ϒ while increasing the secretions of TNF-α and the cytokines, IL-10 and 4, the important cytokines that are expressed at higher levels with increased proliferation and activation of survival pathways, Akt and NF-kB (Paβlack et al.

2016; Nappo et al. 2017). On the other hand, another study presented totally the opposite findings. In the study, let alone L-arginine increases the risk of tumor growth, 2.5 g/Kg supplementation for 20 d inhibited the growth of 4T1, the murine mammary carcinoma cells in mice, while increasing IFN-Y, TNF-α and NO levels in mice (Cao et al. 2016). Opposite to the findings of the study, colorectal cancer cells, in one of the other studies, failed to grow in arginine-free medium and dietary arginine deprivation slows the growth of cancer cells. Moreover, arginine-degrading enzymes, pegylated arginine deiminase (ADI-PEG20) (with the process of pegylation, the process of both covalent and non-covalent attachment of polyethylene glycol polymer chains to arginine molecules) which degrades arginine to citrulline and ammonia and recombinant human arginase-1 (rhArg1peg5000) which degrades arginine into urea and ornithine, may be promising to suppress the growth of these cancer cells by decreasing the arginine concentrations which are required for their growth (Alexandrou et al. 2018). But, the arginine deprivation therapy can only be available for the tumours that are deficient in the urea cycle enzymes like argininosuccinate synthase-1 (ASS1) and ornithine transcarbamylase (OTC), which synthesize arginine. Otherwise, cancer cells can synthesize arginine from citrulline and L-ornithine which are exist in meat and meat products, milk and dairy products, fish and marine origine food products. The deprivation of all these nitrogen rich foods to limit arginine, sooner or earlier, may have important severe side effects like immunosuppression which may result in a much worse prognose. Briefly, though there are some conflicted claims about the effect of arginine in cancer, the therapy which is based on the arginine deprivation is not effective for all types of cancer cells while such trends may always have to cause severe side effects by weakening the immune system. The most important detail in the therapies which target arginine deprivation is the rhArg1peg5000 antagonism with oxaliplatin and 5-fluouracil (5-FU), whereas ADI-PEG20 synergizes (Alexandrou et al. 2018). Meanwhile, the deficiency of arginine switches the energy pathway from aerobic glycolysis (the Warburg effect) to glutamine anaplerosis and oxidative phosphorylation, both of which results in increased oxygen consumption while decreasing fermentation (Kremer et al. 2017). Therefore, cancer cells can also

produce energy by oxidative phosphorylation and glutamine anaplerosis by using glutamine no matter how hard the deprivation of arginine is severe for cancer cells. Glutamine acts as a precursor to produce NADH, NAD+, ATP during its convertion to α-ketoglutarate, malate, citrate and finally pyruvate, ornithine, arginine, serine, glycine, cysteine and asparagines. The last six substances are the initial ones which are utilized by cancer cells as nitrogen donors for protein and nucleotide synthesis. One of the most significant points is formed during the convertion of glutamate to α-ketoglutarate and NADH, NAD+ and finally ATP productions during the convertion of α-ketoglutarate to succinyl-CoA, since these convertions induce TOR complex 1 (TORC1) which results in cancer cell growth and proliferation (Wise and Thompson 2010). Briefly, the arginine and glutamine utilization by cancer cells are the main parts of Warburg effect to be able to make a better adaptation. The paradoxical part is that both of the amino acids are indispensable for the growth and proliferation of not only cancer cells but also immune cells, e.g. lymphocytes and macrophages (Calder and Yagoob 1999). It may be crucial to point out that there is a close correlation between the overexpression of Her2 of cancer cells and the increase in glutaminolysis (Youngblood et al. 2016). Furthermore, arginine and glutamine and their association with cancer can not be evaluated as independently since arginine can be synthesized from glutamine to save concentration of NO which is essential for vascular relaxation (Arnal et al. 1995). In addition to the important role of glutamine in NO production and vessel relaxation, its intraperitoneal injection (0.4 g/Kg/d for 21 d during chemotherapy period) lowers the levels of MMP-2 and MMP-9 while increasing the immunoglobulins, IgA, IgG and IgM and levels of T lymphocytes, CD3+, CD4+ and CD4+/ CD8+, in patients with advanced gastric cancer (40-75 years of age, 94 male and female, 47 control, 6 moth of follow up). Confirming these results, the incidence rate of nausea and vomiting, oral mucositis, thrombocytopenia, abdominal pain and diarrhea were significantly lower after 6 months (Wang et al. 2017). Similar to glutamine, L-arginine supplementation (25 g/d for 7 days) significantly enhances CD4+ T-cell proliferation response (5.03, 1.11-8.95, 95% CI vs. 0.40, 0.17-0.95, OR: 0.40) in the wide-spectrum meta-analysis of 11 trials involving 321

patients from 1966 to 2013 (Kang et al. 2014). These observations and findings have significant importance since they clearly inform the crucial protective effect of glutamine and arginine, particularly on gastric and intestinal mucosal barrier by lowering MMP levels and activating T cell proliferation. More important is that, it has an important improving effect on immune system of the patient with cancer. On the other hand, similar to the triggering effects of glutamine, arginine and NO on the anti-apoptotic signalings, PI3K and Akt, both amino acids also stimulate the expression of VEGF (Morques et al. 2013) and are contraindicated with the FDA proved mTOR and PI3K inhibitors; temsirolimus, everolimus, idelalisib and capanlisib (Janku et al. 2018; Bernfeld et al. 2018). The limitation of arginine during cancer by avoiding from arginine richest foods, e.g. 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, Release 28), might be beneficial during the treatments which administer 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). Like arginine and glutamine, one of the end products of the two amino acids, NO, promotes vascular permeability, endothelial cell proliferation and stimulation of angiogenic growth factors, each of which contributes to cancer progress (Lind 2004). One other crucial finding about the 'dose' factor which makes NO 'cancerogenic' or 'anticancerogenic' is the down-regulation of the antiangiogenic protein TSP1 by the low dose of NO (0.1 μM) which results in the induction of the pro-growth signal, ERK (Extracellular signal-regulated kinase). On the other hand, the higher sustained doses of NO, e.g. 1000μM, induce up-regulation or phosphorylation of the signaling molecules, p53-Ser-15P and MKP-1, which arrest growth and hence, induce the programmed cell death, apoptosis (Ridnour et al. 2005; Roberts 1996; Dameron et al. 1994; Klein-Soyer et al. 1997). NO from 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). Similarly, glutamine has inducing effect on the expression of anti-apoptotic signaling, Foxo3, by astrocytes (Fluteau et al. 2015). On the other hand, glutamine inhibits NF-kB activation and inflammatory cytokine expression by inhibiting Cul-1 (the protein to degrade the target pro-inflammatory protein, IKB neddylation) neddylation. Glutamine prevents this activation of NF-kB via the inhibition of Cul-1 neddylation with NEDD8 (Singleton and Wischmeyer 2008). Therefore, glutamine has significantly important protective effect on immune system by attenuating inflammation, inhibiting the activation of NF-kB and expression of inflammatory cytokine, IKB, which are caused by the Cul-1 neddylation. The closest amino acid to glutamine in effect and structure, arginine (10 μM, N-nitro-L-arginine methyl ester), upregulates the expression of the anti-apoptotic protein, mTOR, by phosphorylating it (Wang et al. 2018), while the higher blood arginine concentrations were found to be closely associated with the incidence of Her2+ breast cancer (5.96, 3.76-12.47, 95% CI vs. 12.54, 7,14-24.94, P:0.000) (Hu et al. 2016). Like arginine, glutamine forms its cancerogenic potential via the induction on mTOR and Her2. The transporter of glutamine, SLC1A5, is expressed more in human Her2+ type breast cancer (Kim et al. 2013). One other paradox from the many others in cancer nutrition is that, not only arginine but also alanine, serine and cysteine enter into the structure of SLCIA5 and mediate glutamine uptake (van Geldermalsen et al. 2016). At the current point and under the highlight of all these findings, although the effects of glutamine and arginine restriction have been found to be suppressive on cancer cells, it is pretty unlikely that the limitation in the intakes of each of the two amino acids will have significant consequences in practice. Firstly, cancer cells try every pathway to adopt to hard conditions and their skill to cope with very different circumstances is excellent. Confirmingly, glutamine limitation does not necessarily inhibit cancer cells, but sometimes may induce the growth of cancer cells via the induction of Her2 and mTOR. Inhibition of glutaminolysis or transamination impairs glutamine-mediated mTORC1 reactivation. But this impairment creates a signal to glutamine to reactivate mTORC1, specifically through the convertion of mTORC1 to glutamate and

restoration of non-essential amino acid pool. Despite a drop in amino acid pool during the limitation of glutamine, the crosstalk between glutamine and autophagy restores insulin sensitivity of mTORC1 which in turn converts it into glutamine (Tan et al. 2017). Moreover, arginine is synthesized from citrulline by argininosuccinate synthetase and argininosuccinate lyase while citrulline is produced through the breakdown of glutamine (Marini 2017). Arginine and citrulline, as the precursors of glutamine, and alanine, serine and cysteine, the three of the amino acids, which mediate glutamine uptake, are indispensable amino acids to improve immune system. While cancer cells use different metabolism processes than normal cells do and successfully escape immune recognition and create an immune-suppressive microenvironment, arginine and its downstream metabolites (e.g., ornithine and citrulline) are essential to T cell activation. This activation modulates immunity to promote tumor survival and growth (Kim et al. 2018). The ability of cancer cells to utilize glutamine to activate TOR kinases for their proliferation and growth, and synthesize glutamine from arginine, citrulline, alanine, serine, cysteine and even glucose (Wise and Thompson 2010) is the initial barrier for the treatments which are based on the limitation of L-arginine and glutamine, other related amino acids and glucose. The attribute of cancer cells to be able to produce ATP from glucose in case of arginine deficiency via glutamine anaplerosis is another obstacle which may limit the benefit of such trends. Additionally, cancer cells can also exploit some important metabolites like itaconic acid which is produced by glutamine anaplerosis (Weiss et al. 2018). The production of itaconic acid significantly potentiates tumor growth by improving the phagocytic ability of cancer cells. Briefly, the explanation for the drawbacks of the restrictions of arginine and glutamine in the diet during chemotherapy and in cancer nutrition is that glutamine can be synthesized from other amino acids including L-arginine and even glucose while the limitation of glutamine can be exploited by cancer cells in which they can convert mTOR to glutamine under Warburg effect in case of glutamine deprivation. Furthermore, it should never be neglected to remember that limitation of glutamine or arginine and the related amino acids in diet under the pretext of reducing the over-expression of itaconic acid synthesis by

cancer cells, may also have more harmful effects than its benefits. Because the metabolite is not only exploited by cancer cells, but it is essential for the immune system. Briefly, it is a strong possibility that an approach which restrics the intake of glutamine and other related amino acids, the amino acids which are indispensable for the immune system, can not be useful in parctice. Cancer cells will continue to have glutamine production by using the other amino acids and glucose under the influence of Warburg effect. Futhermore, the deficiency of glutamine and arginine will continue to stimulate insulin secretion. The approach which limits the important nutrients will have to suppress and weaken T cells and the already weakened or collapsed immunity of the patient with cancer. But, these details should not be evaluated that an arginine or glutamine rich nutrition program should be followed in patients with cancer. Because of the inducing effect of glutamine and arginine on mTOR, PI3K and HO-1, a rich nutrition in each of the two amino acids should be limited or avoided during the administrations of mTOR, PI3K and HO-1 inhibitors. In spite of the inhibitory effects of high dose arginine supplementation or nutrition (≥400 μM) on IL-6, -8, -10, HO-1 TNF-α and COX-2, the problem here is the maintenance of the ≥400 μM rich arginine concentrations in blood and microenvironment of tumor. The studies which claim such inhibitory effects could obtain these high concentrations in their methodology which used cancer cell lines under laboratory conditions. But, there is no any standard nutrition or diet to reach to the mentioned high arginine concentrations in tumor microenvironment. These standards can not be formed easily in practice because of the great differences in genetics, stomach barrier, bioavailability of the nutrients in diet, the composition of the components in diet, pH, concentrations of gases in blood and tumor microenvironment and many other intrinsic and extrinsic factors, all which effect the concentration. Therefore, although the rich arginine concentrations, ≥400 μM, have inhibitory effect on IL-6, -8, -10, HO-1, TNF-α and COX-2, limitation of arginine and glutamine during the administrations of the inhibitors of IL-6, -8, -10, HO-1 NTF-α and COX-2, would have been a much more precautionary approach to be able to prevent the risk of any contraindication with these inhibitors. The limitation of the two amino acids may particularly be useful during the administrations of

the inhibitors of PI3K, VEGF and Akt, since the amino acids and NO activate the expression of these anti-apoptotic proteins. The effects of arginine, glutamine or NO on IFN-Ɣ, TNF-α, Foxo-3 and MMP are still not clear and need to be highlighted with further studies. Therefore, the limitation of the amino acids may expectedly be beneficial to avoid from any risk of contraindication with the inhibitors of IFN-Ɣ, TNF-α, Foxo-3 and MMP, until their effects on these proteins are determined. Finally, it should never be neglected to consider that the limitations of the amino acids may be precautious measures to be able to prevent any contraindication with the chemotherapeutic agent, but only during chemotherapy period. Although the present status of the amino acids and NO in anticancer nutrition is very controvertial, what is definite about both amino acids is that they are essential and indispensible for immune system. For this reason, a nutrition rich in these amino acids should continue followed by the exceptional chemotherapy periods.

9

HER2, ITS ASSOCIATION WITH FOOD BIOACTIVE COMPOUNDS, DRUG INTERACTIONS, MMP, FOXO3, NF-KB, IL-6/STAT3, IL-8, PI3K/AKT, MTOR AND MDR1 IN CANCER

Human epidermal growth factor receptor 2 (Her2), a member of the epidermial growth factor receptor family which has tyrosine kinase activity, is one of the most important receptors. Its dimerization results in the autophosphorylation of tyrosine residues in the receptor. The dimerization initiates various signaling pathways which lead to cell proliferation and tumor growth. Activation or overexpression of the receptor does not only appear in breast, gastric and gastroesophageal, but also ovary, endometrium, bladder, lung, colon and head and neck cancers (Iqbal and Iqbal 2014). One of the crucial effects of MMP, the membrane-type 1 matrix metalloproteinase (MT1-MMP), a cell surface cancerogenic protease which is expressed in bone marrow stromal cells, induces Her2. The abnormal expression of Her2 with Ezrin (an important member of the ERM, Ezrin-radixin-moesin which is the cytoskeleton-associated protein family and the protein which is a transit between membrane and actin proteins) and c-MET (the tyrosine kinase receptor for hepatocyte growth factor, HGF), has often been associated with the poor prognosis in gastric adenocarcinoma (Bretscher et al. 2002; Salgia 2009 and Shan et al. 2013). The initial reason for the bad prognose is most likely due to the promoter region of MMP-9 between -2500

and -2000 bp which upregulates Her2-mediated transcription (Shan et al. 2015). So, the close relation between MMP and Her2 appears as a novel molecular marker in tumor invasion (Pellikainen et al. 2004). Her2 is strongly dependent not only on MMP, but also the two of the oncogenic signalings, PI3K/Akt and MAPK/ERK (Figure 2), while breast cancer is biased toward PI3K-dependence and cancers of lung, ovarium and stomach are particularly MAPK-dependent via HER2 (Kirouac et al. 2016). Saponins of *Astragalus membranaceus*, a traditional medicinal herb which is rich in polysaccharides, anti-oxidants, anti-inflammatory flavonoids and saponins with anti-cancerogenic effects, have been informed to inhibit the overexpression of both MMP and Her2 (Auyeung et al. 2016). The ethanol extract of *Astragalus membranaceus* and its active saponins, campanulin, ononin, calycosin and formononetin (100 μg/mL/48h, in the human breast cancer cell lines, MCF-7, SK-BR-3 and MDA-MB-231) (Zhou et al. 2018), afrocyclamin A (a triterpene saponin which is isolated from Androsace umbellate, 20 μM/24h, in the human prostate cancer cell lines, DU145, LNCaP and PC-3) (Sachan et al. 2018), lycopene and its rich sources (lycopene, 80 μM/168h, in breast cancer cell lines, MCF-7, SK-BR-3, MDA-MB-468) (Takeshima et al. 2014), EGCG and its sources (EGCG, 1 μM/48h in the breast cancer cell lines, T47D and MDA-MB-231) (Zeng et al. 2014), apigenin and its rich sources (apigenin, 50 μM/72h, in the breast cancer cell line, MCF-7) (Scherbakov and Andreeva 2015), quercetin and its rich sources (quercetin, 60 μM/72, in the human breast cancer cell line, BT474) (Seo et al. 2016), sulforaphane and its rich sources (sulforaphane, 10 μM/24h, in the human ovarian cancer cell line, A2780) (Kan et al. 2018), I3C and its sources (I3C, 200 μM/48h, in the human breast cancer cell line, MCF-10AT-Her2) (Tin et al. 2014), α-tocopherol and its sources (α-tocopherol, 50 μM/24h, in ErbB2-overexpressing human mammary carcinoma cells) (Wang et al. 2005), genistein and its sources (genistein, 100 μM/48h, in the human breast cancer cell line, BT-474) (Sakla et al. 2007), genistein as combined with tamoxifen (genistein, 25 μM as combined with tamoxifen, 5 μM/46h, in the human breast cancer cell line, BT-474) (Mai et al. 2007), Gemini vitamin D analog BXLO124 (1 alpha, 25 – dihydroxy - 2OR – 21 (3 – hydroxyl – 3 - deuteromethyl, 4,4,4 - trideuterobutyl) – 23 – yne - 26, 27 – hexafluoro -cholecalciferol)

(BXLO124, 0.3 μg/Kg, intraperitoneal injection 3 times/week for 54 weeks or 100 nM in MMTV-ErbB2/neu transgenic mice mammary cells) (Lee et al. 2010), and astaxanthin (50 μM/24h, in the breast cancer cell line, MCF10A, the natural sources are; algae, yeast, salmon, trout, krill, shrim and crayfish and its sources in plant origin; *Haemotococcus pluvialis*, *Chlorella zofingiensis*, *Chlorococcum* and *Phaffia rhodozyma* while *H. pluvialis* is currently in wide public consumption) (McCall et al. 2018; Ambati et al. 2014), are the food/plant bioactive compounds which inhibit the receptor, Her2. On the other hand, lapatinib (GW572016) (Chu et al. 2005), neratinib (Burstein et al. 2010), canertinib (Allen et al. 2002), CP-724714 (Jani et al. 2007), sapatinib (AZD8931) (Hickinson et al. 2010), CUDC-101 (Lai et al. 2010), tryphostin B42 (Soto-Cruz et al. 2008), afatinib (Suzawa et al. 2016), TAK-285 (Nakayama et al. 2013), AC480 (BMS-599626) (Soria et al. 2012), AEE788 (Evans et al. 2010), trastuzumab (Komarova et al. 2011), ado-trastuzumab emtansine (Guerin et al. 2015), pertuzumab (Harbeck et al. 2013) and dacomitinib (Oh et al. 2016), are the most commonly administered chemotherapeutic agents which target the receptor. Accordingly, the mentioned food bioactive food/plant bioactive compounds and their rich sources in food and plant origin might be useful to support and enhance the anticancerogenic potential of the chemotherapy which administers one of the mentioned Her2 inhibiting drugs by creating a synergism. On the other hand, there is no study which uses cancer cell lines about the direct effect of ascorbic acid and beta carotene on the gene. The status of L-arginine and resveratrol currently seems very critic since both of the food bioactive compounds might be contraindicated with the Her2 inhibitors. L-arginine continues to be one of the most controvertial and debated amino acid with its effect on the receptor because of its dual effect. The treatment of the fibroblast cell line, NIH3T3, with the amino acid (7 mM/24h), activates the anti-apoptotic signalings and proteins, ERK1/2, Akt, PI3K, which are always activated concurrently with Her2 (Fujiwara et al. 2014). On the other hand, the arginine levels of 234.190 patients with Her2+ breast cancer are informed to be significantly lower than those of control patients (5.95, 3.76-12.47 vs. 12.54, 7.14-24.94, 95% CI) (Hu et al. 2016). The authors of the wide scale analysis argue the possible reason as the

remarkably different molecular subtypes of the cancer. When the effect of arginine is considered, the triggering effect of L-arginine may be due to its effect on not only Her2, but also mTOR, mTORC1, NF-kB and Rheb. Confirmingly, arginine, (10 μM) and supplementation with the amino acid (0.6 %) in pig diet for 7-14 days activate mTOR (Yao et al. 2008; Saxton et al. 2016). On the other hand, arginine can activate GCN2 kinase (a serine/threonine protein kinase that senses amino acid deficiency through binding to uncharged transfer RNA). Increased levels of GCN2 protein by high intracellular arginine concentrations distrupt the formation of GCN2/β-arrestin (the negative regulator proteins of G-protein-coupled receptors, GPCR), and the signaling of NEDD4 (neural precursor cell expressed developmentally downregulated gene 4-like, an enzyme which down regulates the epithelium sodium channel, and as a result, causes apoptosis in cancer cells) (Ma and Pei 2007). So, the effect of the amino acid on GCN2 and NEDD4 may be the other factors for the cancerogenic potential of the amino acid. On the other hand, the combination of L-arginine with α-PD-L1 antibody, the antibody to inhibit the programmed death-ligand which suppresses the CD8+ T cell proliferation and subsequently immune system, is informed to be promising in osteosarcoma (He et al. 2017). In addition to the cancerogenic and anticancerogenic potentials of the amino acid, it may be useful to remind once more that L-arginine has significantly important boosting effect on immune system which makes it indispensable, not only for the patients with cancer, but for all individuals. The amino acid promotes the function of immune cells by facilitating T-cell proliferation and survival. It also elevates the number of splenic CD8+ T-cells, the serum interferon-Ɣ and CD8+ T cells. Briefly, there should be a cautious approach for the intake of the amino acid especially during the administrations of Her2/ERK1/2/Akt/PI3K inhibitors, but the indispensable and crucial role of the amino acid on immune system for other chemotherapies and healthy individuals should never be neglected.

10

ARGININE INDUCED-MTOR AND ITS ASSOCIATION WITH CANCER AND NUTRITION

Among the contributers to the cancerogenic potential of arginine, mTOR is crucial. mTOR, a serine/threonine kinase that belongs to the anti-apoptotic protein family, PI3K, and its catalytic subunit, mTOR comlex 1 (mTORC1) (TORC1 component regulatory-associated protein of mTOR), are in close relation with Rag GTPase, the binding protein of Raptor which is required for lysosomal localization of mTORC1. Both of PI3K and mTOR are activated by arginine and this activation results in the recruitment and activation of mTOR in the lysosomal surface of mTORC1. The activation of mTOR localizes Rheb and controls the transduction of external signals to cytoplasmic and nuclear effectors (Yao et al. 2017; Cardama et al. 2017). mTOR is also important key effector of another anti-apoptotic signaling Akt while mTOR downstream from Akt controls the inflammatory and anti-apoptotic protein, NF-kB. Akt induces NF-kB by using mTOR-associated protein Raptor (Dan et al. 2008). mTOR, Her2 and NF-kB inhibitors are often in a very close relation while either of Her2 or mTOR downstreams the anti-apoptotic signaling, PI3K/Akt (Rosen and She 2006; Pegram et al. 1999). Based on the triggering effect of Her2 and mTOR on tumor growth, the following mTOR inhibitors have continued to gain a trend in cancer treatments. These are; rapamycin (Kennedy and Lamming 2016, wortmannin (Bridges et al. 2012), NVP-BEZ235 and RAD001 (each one solely inhibits mTOR while the inhibition is stronger in their combined

use) (Nyfeler et al. 2012), CCI-779 (Teachey et al. 2006), AZD8055 (Chresta et al. 2010), INK128 (Zhang et al. 2015), OSI-027 (Chen et al. 2019), dual PI3K-mTOR inhibitors; NVP-BEZ235 (Xin et al. 2017), omipalisib (GSK2126458) (Basu et al. 2018) and XL765 (SAR24509) (Gravina et al. 2016). When the food/plant bioactive compounds which have anticancerogenic potential by inhibiting mTOR are considered, these are; theopylline (5 mM/30 min., on adipocyte cell line, 3T3-L1, namely sources; coffee, tea and cacao) (Scott and Lawrence 1998; Franco et al. 2013), caffeine 25 mM724h in the bone marrow neuroblast cell line, SH-SY5Y, namely sources are; coffee, cacao and chocolate) (Saiki et al. 2011), rotundarpene (the extract from the stems of Ilex rotunda, an evergreen tree from the family, *Aquifoliaceae*, 25 μM/24h, in the keratinocyte cell line, HEK001) (Kim et al. 2017), resveratrol (100 μM/4h, in the human embriyonic kidney cell line, HEK293 and human cervical carcinoma cell line, GFP-LC3 Hela) (Park et al. 2017), lycopene (100 μM/72h, from the breast cancer cell lines, only inhibited MDA-MB-468, but not MCF-7 and SK-BR-3 cells!) (Takeshima et al. 2014), amygdalin (5 mg/mL/48h, in the NSCLC cell lines, H1299/M and PA/M) (Qian et al. 2015), genistein (100 μM/72h, in the endometrial cancer cell lines, ECC-1 and RL-95-2) (Malloy et al. 2018), EGCG (80 μM724h, in the human embryonic kidney cell lines, HEK293T, ATCC, CRL-3216) (Holczer et al. 2018), sulforaphane (5 μM/24h, in vascular smooth muscle cells) (Shawky and Segar 2017), ascorbic acid (200 μmoL/L/48h, in mesechymal stem cells) (Yang et al. 2018), quercetin and apigenin (40 μM/12h each, in the hepatocellular carcinoma cell line, HepG2) (Yang et al. 2018), luteolin (20 μM/24h, in the cellosaurus cell lines; A431-III and A431-P) (Chen et al. 2018), ϒ-tocotrienol (4 μM/96h, in the mammary cancer cell line,+SA and 10 μM/96h and in the mammary cancer cell line, MCF-7) (Parajuli et al. 2015), 1,25-dihydroxyvitamin D3 (1000 nM/48h, in the immortalized human uterine fibroid cell line, HuLM, and immortalized human uterine myometrial smooth muscle cell line, U+SMC)(Al-Hendy et al. 2016), curcumin (20 μM/3h with or without piperidine, 20 μM/3h, in the human colon cancer cell lines, HT-29 and Caco-2) (Kaur et al. 2018) and piperine (300 μM/48h, in the prostate cancer cell line, DU145, its rich source; black pepper) (Zeng et al. 2018; Gorgani et al. 2017). So, these compounds might be useful

when they are exist in the diet especially during the administration of mTOR inhibitors by creating a synergism to inhibit the enzyme. Although there is currently no study about the effect of folate on mTOR, maternal deficiency of folate in rat inhibits placental mTORC1 signaling (Rosario et al. 2017). Under the highlight of the findings, it may be a precautious and smart measure to limit the folic acid rich food consumption until studies to analyze the effect of the provitamin on the receptor in cancer cell lines are carried out. The findings of Takeshima et al. (2014) about the effect of lycopene on mTOR should be concerned with a high priority since they clearly indicate to the importance of the factor of 'sub-type' in cancer cells, even in one type of cancer, like in the inhibitory effect of lycopene on only the sub-type of breast cancer, MDA-MB-468, while it does not have any effect on other sub-types (MCF-7 and SK-BR-3) of the same cancer type, 'breast'. Finally, there is currently no study about the effect of beta-carotene and lycopene on the receptor and the association of them with mTOR needs to be studied urgently. Finally, in spite of their indispensable and crucial role on immune system, the intake of arginine and other amino acids should be cautiously concerned during the mTOR and Her2 inhibitor administrations. Arginine (1 mM/36h, in C2C12 mouse myoblasts) enhances protein synthesis by phosphorylating mTOR in a nitric oxide-dependent manner (Wang et al. 2018). The supplementation with the amino acid (0.6 %) in piglets after 7th day increases mTOR signaling activity in their skeletal muscle (Yao et al. 2008). The amino acid (~30 μM) distrupts the complex of Castor1 (a protein which is a specific arginine sensor) with Gator2 (a GTPase activating protein) by binding to Castor1. Gator2 becomes free and activates mTOR. In arginine deprivation, Gator2 is bound to Castor1 in the complex and therefore it is not functional. This mechanism may be the reason for the inducing effect of the amino acid on mTOR (Chantranupong et al. 2016). All these findings clearly indicate to the inducing effect of the amino acid on mTOR and its signaling. Therefore, the limitation of arginine and other amino acids with the same effect may be a smart and cautious approach and measure, especially during the administrations of the mTOR and Her 2 inhibitors.

11

AN IMPORTANT CORNER, FOXO3, IN APOPTOSIS AND ITS ASSOCIATION WITH DRUGS AND FOOD/PLANT BIOACTIVE COMPOUNDS

Foxo3, the gene and transcription factor, functions as a trigger for apoptosis through upregulation of the other pro-apoptotic proteins such as Bim, Bax and PUMA (Ekoff et al. 2007; Harada and Grant 2012). On the other hand, because the inhibition of Akt/PI3K promotes the apoptotic effect of Foxo3 (Das et al. 2016), Akt/PI3K inhibiting food/plant bioactive compounds might be in synergism with the drugs which induce Foxo3, namely; STI571 and paclitaxel as combined (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) and 5,aza-deoxyctidine (Geiger et al. 2012). It may also be useful to remind that the Foxo inducing and Akt/PI3K and Her2 inhibiting food/plant bioactive compounds and their rich sources during the administrations of the Her2 inhibitors may be beneficial since Her2 activates PI3K/Akt signaling which directly suppresses Foxo1/3 (Carpenter and Lo 2013). The Foxo1/3 inducing food/plant bioactive compounds which might be in synergism and therefore enhance the anticancerogenic potential of the Akt/PI3K inhibiting and Foxo inducing drugs are; berberin (a benzylisoquinoline alkaloid which is extracted from a wide range of medicinal plants, e.g. *Berberis vulgaris*, *Berberis aristata* or in its English name, barberry and tree turmeric) (100 μM/72h, in the NSCLC cell

lines, A549, PC9, H1650 and H1299) (Zheng et al. 2014), sulforaphane (30 μM/48h, in the pancreatic cancer cell lines; PANC-1, MIA PaCa-2, Hs766T and ASPC-1) (Roy et al. 2010), quercetin (50 μM/24h, in the oral squamous carcinoma cell lines, HSC-3 and TW206) (Huang et al. 2013), resveratrol (the rich nutrition in resveratrol in diabetic rats by increasing Sirt 1, a nicotinamide adenosine dinucleotide-dependent deacetylase that removes acetyl groups from various proteins) (Wu et al. 2012; Rahman and Islam 2011) (100 μM/24h, in the human melanocytes by increasing Sirt 1) (Kwon et al. 2017), genistein or daidzein (400 μM/48h, in the colon cancer cell line, HT-29) (Liang et al. 2018), ascorbic acid, α-tocopherol, kaempferol, fisetin, hesperetin, naringenin (either of each; 200 μM/24h, in the human embryonic kidney cell line, Hek-293) (Pallauf et al. 2017), apigenin or luteolin (100 μM/24h, in the human osteosarcoma cell line, U-2OS) (Bumke-Vogt et al. 2014), lycopene (oral administration at a dose of 10 mg/Kg/body weight/day for 5 days, protected mice keratinocytes from UV damage by decreasing Akt and inducing Foxo3a) (Chen et al. 2017), EGCG (600-1000 μM/day for 12 days, in *Caenorhabditis elegans*, a free-living transparent nematode that lives in temperate soil environments) (Xiong et al. 2018), cTet (the I3C cyclic tetrameric derivative, 8 μM/72h, in the breast cancer cell lines, MDA-MB-231 and BT-20, MCF-7 and BT-474) (De Santi et al. 2011) and I3C (600 μM/48h, in the human osteosarcoma cell lines, MG-63 and U2OS) (Lee et al. 2018). There is still no study about the effect of amygdalin on Foxo. The methylation of Foxo1 at arginine248 and Arginine250 directly blocks Akt-mediated phosphorylation of Foxo1 at serine253 and leads to decrease in oxidative stress-induced apoptosis depending on the PI3K-Akt signaling pathway (Yamagata et al. 2008). Therefore, the limitation of arginine (and also glutamine and NO) rich foods during the treatment with Foxo1/3 inducing or Akt/PI3K inhibiting drugs may be a smart approach by lowering the risk of the inhibition of Foxo and induction of Akt/PI3K signaling as a result of arginine methylation of Foxo. On the other hand, there is no study which analyses the effect of arginine as time and dose depented in cancer cells.

What seems crucial about Foxo and cancer lies between ATP production of cancer cells, the expression of Foxo and TNF-α. ATP can selectively

decrease the expression of Foxo1/3 via the phosphorylation of epidermal growth factor receptor (EGFR) and Akt, while the ATP production of cancer cells does not have any effect on the expression of Foxo4/6, EGFR, Akt and ERK1/2, all of which are involved in the release of TNF-α which is induced by ATP. On the other hand, the overexpression of Foxo3a can inhibit the release of TNF-α which is increased by ATP production of cancer cells. This means that cancer cells with their ATP production suppress Foxo1/3 expression by inducing EGFR. The detail may be vitally important and a prognose determiner during cancer treatments and nutrition since the findings clearly point out that Foxo1/3 inducing drugs and food/plat bioactive compounds are in complete synergism with the TNF-α/EGFR/PI3K/Akt inhibiting drugs and food/plant bioactive compounds. Other words, Foxo inducing and Akt/PI3K/TNF-α/EGFR inhnbiting food/plant bioactive compound rich nutrition may help to a better prognose, creating a synergism to protect from aberrant sgnalings which are formed due to the cancer cells which produce ATP.

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PUMA, BCL-2, BAX AND THEIR ASSOCIATION WITH NUTRITION

The gene of PUMA encodes two BH3 domain containing proteins, PUMA-α and PUMA-β, both of which are induced in cells following p53 activation. The two protein bind the anti-apoptotic member of Bcl-2 family, Bcl-2, to induce the release of cytochrome c and activate the induction of the programmed cell death, apoptosis (Nakano and Vousden 2001; Lomonosova and Chinnadurai 2008). The p53 upregulated modulator of apoptosis, PUMA, is also known as Bcl-2 binding component 3 (BBC3). It is a pro-apoptotic protein and member of the Bcl-2 protein family. PUMA also initiates apoptosis in part by dissociating Bax and Bcl-xL and promoting Bax multimerization and activation. Its mitochondrial translocation induces release of cytochrome c (Ming et al. 2006; Jabbour et al. 2009). So, Bcl-2 inhibition in addition to the induction of PUMA and its pro-apoptotic members, Bax and Bcl-xL and anti-PUMA-antibodies which recognize PUMA, have often been the new promising targets to induce apoptosis in cancer treatments. The member, Bcl-2, often acts as anti-apoptotic, while Bax is a pro-apoptotic protein (Nakamura et al. 2003). Accordingly, the Bcl-2 inhibitors; venetoclax/ABT-199, navitoclax/ABT263, S64315/MIK665, S55746/BCL201 (Campbell and Tait 2018; Casara et al. 2018), might have benefited from the following PUMA and Bax inducing food/plant bioactive compounds to maintain a much higher rate of apoptosis. These Bax inducing and Bcl-2 inhibiting food/plant bioactive compounds are; quercetin (2.5 mg/mL, on endometrial cells by oral gavage in pregnant

mice) (Xiaodan et al. 2016), sulforaphane (12 μM/L/48h, in the human acute myeloid leukemia cell lines KG1a and K562) (Wang et al. 2018), resveratrol (200 μmol/L/24h, in the lung adenocarcinoma cell line, A549) (Wang et al. 2015), I3C (100 μM/72h, in the breast cncer cell lines, MCF10A and MCF10CA1a) (Sarkar et al. 2003), apigenin (160 μM/48h, in the human lung cancer cell line, 549) (Lu et al. 2010), ascorbic acid (500 μg/mL/96h, in the cellosaurus cancer cell lines, HuT-102 and C91-PL, the peripheral blood T lymphocyte cell lines, CEM and Jurkat) (Harakeh et al. 2007), kaempferol (200 μM/72h, in the gastric cancer cell lines, MKN28, SGC7901 and GSE-1) (Song et al. 2015), vitamin D_3 (its supplementation in human as 400 IU twive daily for 6 months, in the crypt opening to the colon lumen) and elemental Ca (as 2.0 g as combined with 800 IU vitamin D_3 daily for 6 months, in the crypt opening to the colon lumen) (Fedirko et al. 2009), poly-L-arginine (60 mg/L/24h, in the human lung mucoepidermoid carcinoma cell line, NCI-H292) (Wang et al. 2018) and amygdalin (10 mg/mL/24h, in the prostate cancer cell lines, DU145 and LNCaP) (Chang et al. 2006). Opposite, genistein (its supplementation in rat as 5-20 mg/body weight/ day for 15 days, in granulose cells) (Chi et al. 2018), folic acid (1000 nmoL/L/24h, in HUVECs) (Cui et al. 2018), lycopene (4 mg/Kg/d as gavages for 8 weeks in rat) (Soleymaninejad et al. 2017) and EGCG (its supplementation in rats as 20 mg/Kg body weight/day for 12 weeks by oral gavage) (Adikesavan et al. 2013) inhibit the pro-apoptotic Bax while inducing anti-apoptotic Bcl-2 and increasing the ratio of Bcl-2 to Bax. Sulforaphane may be included to diet during Bax/PUMA inducers and Bcl-2 inhibitors since the findings of Wang et al. (2018) (sulforaphane, 12 μmoL/L/48h, in the human leukemia cell lines, KG1a and K562) and (Zhou et al. 2017) (sulforaphane, 5 μg/mL/72h, in the Xuanwei lung adenocarcinoma cell line, XWLC-05) claim the Bax and PUMA inducing effect and Bcl-2 inhibiting effect of the flavonoid. Opposite, genistein, EGCG, lycopene and folic acid rich foods, because of their Bcl-2 inducing and Bax/PUMA inhibiting effects, should be limited or avoided during and after the administrations of Bcl-2 inhibitors and Bax/PUMA activators (Figure 3). The PUMA inducing food/plant bioactive compounds with the current data are; sulforaphane, I3C (60 μM/48h, in the human B cell precursor acute lymphoblastic leukemia

cell line, NALM-6) (Safa et al. 2015), resveratrol (200 μM/72h, in the human pancreatic cancer cell lines, PANC-1, BxPC-3) (Duan et al. 2016), quercetin (30 mg/Kg/day for 2 weeks in mice, in the human gastric carcinoma cell lines, SNU719 and MKN74) (Lee et al. 2016), apigenin (120 μM/24h, in the pancreatic cancer cell lines, BxPC-3 and MiaPaCa-2) (King et al. 2012). But, genistein (200 μM/48h, in the human lung cancer cell line, A549, the immortal cell line, HeLa and the human Caucasian fibroblast-like fetal lung cell line, WI-38) inhibits PUMA according to the findings of Tategu et al. (2008). Their findings are in accordance with the ones which are belong to Chi et al. (2018) who found the inhibitory effect of the soy isoflavonoid on Bax and inducing effect of it on Bcl-2. Therefore, a diet rich in genistein or its supplementation might be contraindicated with the chemotherapeutic agents which target cancer cells by activating PUMA and/or inhibiting Bcl-2. In spite of a plenty number of chemotherapeutics which target cancer cells via PUMA, there is still no data as related to the effects of many important food/plant bioactive compounds, e.g. folat, calcitriol, EGCG, arginine and tocopherol.

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THE PROTEIN COMPLEXES WHICH ARE THE MOST MULTIDIRECTIONAL IN CANCER, NF-KB AND COX-2, AND THEIR RELATION WITH NUTRITION, CANCEROGENIC PATHWAYS, PROTEINS AND SIGNALINGS

NF-kB, the protein complex, utilizes cellular processes by binding to DNA sequences of the genes. NF-kB is also important in cancer progress because of its close relation with metastasis, inflammation and oncogenic mutations. Prolonged chronic inflammation may often cause tissue damage, autoimmune and degenerative diseases which may lead to cancer by enhancing cellular stress, recruiting inflammatory factors and accumulating DNA damage (Xia et al. 2014). There is a close relation between the cancerogenic receptor, Her2, and NF-kB and they often induce each other in cancer while both activate the MAPK/PI3K/Akt signaling (Merkhofer et al. 2010; Bailey et al. 2014). Also, Her2 elevated expressions of the inflammatory and cancerogenic cytokines, IL-8 and IL-6/STAT3, have a close relation with NF-kB, since Her2, IL-8 and IL-6 induce NF-kB (Ancrile et al. 2007; Sparman and Bar-Sagi 2004; Hartman et al. 2011; Wang et al. 2003). Additionally, NF-kB is often transactivated together with PI3K/Akt and IL-8 pathways (Lin et al. 2011). On the other hand, the inflammatory enzyme, COX-2, modulates cell proliferation and apoptosis mainly in solid tumors (Sobolewski et al. 2010). While COX-1 is considered as a housekeeping enzyme to maintain basal prostaglandin levels for tissue homeostasis, COX-2 is an

inducible enzyme which produces prostaglandins in inflammatory and tumorigenic incidences (Greenhough et al. 2009). The important status of COX-2 in cancer stems from its production of the inflammatory prostaglandin, PGE_2, the key product which exerts its effects on cellular processes through the receptor EP1-4 (Epstein Barr Virus, EBV)-mediated tumorigenesis (Gandhi et al. 2015). One of the findings which clearly indicates to the cancerogenic effect of COX-2 followed by inflammation, is the elevated incidence rates in adenomas, adenocarcinomas and lung cancer which are accompanied by COX-2 overexpression (Hasegawa et al. 2001; Jiang et al. 2013). Inflammatory Bowel Disease (IBD) and the elevated COX-2 and PGE2 levels in IBD also appear as a strong contributor to cancer progress (Izzo and Camilleri 2008; Lewis et al. 1999). The most commonly used indicator to prove the close association between COX-2 and elevated risk of cancer is the reduced level of metastasis followed by the prolonged use of non-steroidal anti-inflammatory drugs, NSAIDs (Zhao et al. 2017). But, there are significantly important side effects of them, like nausea, dyspepsia, gastritis, abdominal pain, peptic ulcer, gastrointestinal bleeding and gastroduodenal ulsers (Wang and DuBois 2010). When the effect of NF-kB on the enzyme is considered, NF-kB is an important inducer of COX-2 and both are activated by the inflammatory microenvironment and various oncogenic mutations. Both COX-2 and NF-kB, are in close relation with many of the cancerogenic signalings, proteins and pathways. COX-2 activates the signalings of PI3K/AKT/ Notch and Wnt (Majumder et al. 2016). The carcinogenic cytokine and its precursor STAT3, is also triggered by COX-2 (Rummel et al. 2006), while IL-6/STAT-3 induction by COX-2 activates MMP-9 (Kothari et al. 2014). The enzyme also activates VEGF which results in the progress of lymphangiogenesis in human lung adenocarcinoma via the activations of Her-2, c-Jun NH2-terminal kinase (JNK, a mitogen activated protein kinase) and AP-1, the transcription factor which transduces growth signals to the nucleus) (Su et al. 2004; Chien et al. 2009). The other interaction of the enzyme has been informed as the doxorubicin-induced expression of MDR1 (Multidrug Resistance gene1) and NF-kB (He et al. 2015). NF-kB can also be activated by various stimuli, like cytokines, e.g. TNF-α, IL-1β, Epidermial Growth Factor (EGF), bacterial and viral

products like lipopolysaccharide, UV, ionizing radiation, ROS and oncogenic stress. Any of the stimuli activates the inhibitor of kB(IkB) kinase (IKK) complex. The activated IKK complex causes phosphorylation of IkB which results in the degradation of the complex. NF-kB becomes activated as a result of the degradation of its inhibitor in the complex (Xia et al. 2014). The important point is that the elevated NF-kB levels and pro-inflammatory cytokine accumulations by the effect of any of these stimulants significantly contribute to the formation of a pro-tumorigenic microenvironment. During the formation of the microenvironment, these stimulants and NF-kB might modulate let-7 family of tumor suppressor microRNAs, while inducing IL6/STAT3 pathway (Illiopoulos et al. 2009). The elevated NF-kB activity develops in a TNF-α dependent manner and this association of NF-kB and TNF-α is essential for the later stages of tumor development (Pikarsky et al. 2004). The NF-kB and its association with COX-2 does not play any role without TNF-α, since NF-kB induces TNF-alpha induced COX-2 expression (Ke et al. 2007). NF-kB also controls the gene, MMP-9, and the overexpression and activation of NF-kB induce MMP-9 while NF-kB is induced by the anti-apoptotic gene, Bcl-2 (Ricca et al. 2000). The increase in VEGF secretion in tumours is also correlated with NF-kB activation (Leychenko et al. 2011). Similarly, the activation of the Mitogen Activated Protein Kinases (MAPKs) is formed by PI3K/ Akt, which in turn initiates the activation of NF-kB and ultimately induces COX-2-dependent PGE(2) and IL-6 secretion (Lee et al. 2010) (Figure 3). Finally, the redox-sensitive transcription factor NF-kB connects itself to the proximal promoter of the HIF-1alpha gene, while HIF-1alpha is induced by TNF-α (Görlach and Bonello 2008). Also, cell adhesion molecules namely, selectins, integrins and their ligands are regulated by NF-kB (Collins et al. 1995). Briefly, NF-kB and COX-2 contribute to angiogenesis in a pro-tumorigenic and inflammatory microenvironment, as being in a close interaction and multidirectional manner with many of the cancerogenic signalings, proteins and pathways, including HIF-1 alpha, MMP9, TNF-α, VEGF, c-Jun, IL-1β, AP-1, HER2, PI3K/AKT, Notch, Wnt and IL6/STAT-3. Accordingly, the following chemotherapeutic agents which inhibit both COX-2 and NF-kB; 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), might benefit from the following food bioactive compounds or their supplements with the same effect, by creating a synergism. These food bioactive compounds are; Indole-3-carbinol (I3C) (50 μM/24 h, in the human T-cell leukemia cell line, KBM-5) (Takada et al. 2005), resveratrol (120 μM/10 min, in the human colon adenocarcinoma, HT-29) (Zykova et al. 2008), quercetin (300 μM/48h, in the human endothelial cells, HUVECs) (Xiao et al. 2011), sulforaphane (50 μM/24h, in rabbit articular chondrocytes) (Yu et al. 2013), beta carotene (2.0 μmol/L/24h, in the human colon adenocarcinoma cell lines, LS-174, HT-29, WiDr, and the colon cancer cell line, HCT116) (Palozza et al. 2005), lycopene (30μM/96h, in the human colorectal cancer cell line, SW480) (Cha et al. 2017), apigenin (20μM/8h, in the non-melanoma skin cancer cell line, HaCaT) (Kiraly et al. 2016), arginine (2 mM/24h, in the human colon adenocarcinoma cell line, HT29) (Paduch et al. 2011), genistein (100μg/mL/10h, in the human breast cancer cell line, MCF10A) (Chung et al. 2014), kaempferol (40μM/4h, in non-melanoma skin cancer cells) (Lee et al. 2010), EGCG (300μM/48h, in the colon cancer cell line, HT-29) (Peng et al. 2006), amygdalin (1000 μg/mL/24h, in mouse BV2 microglial cells) (Yang et al. 2007), alpha tocopherol (but not gamma form!!) (50 mM/4h, in the lung cancer cell lines, BEAS-2B, H460 and A549) (Lee et al. 2006), ascorbic acid (100 mM/24h, in the human neurorenal cell line SK-N-SH) (Candelario-Jalil et al. 2006), chrysin (30 mM/6h, in HUVECs) (Zhao et al. 2018), diosmin (100 mg/Kg body weight/7d in blood of diabetic rat, source: citrus family fruits, e.g. lemon and lemon juice, plant: *Teucrium gnaphalodes*) (Ahmed et al. 2016; Barberan et al. 1985), luteolin (50 μM/24h, in the mouse macrophage cell lines; MH-S and RAW 264.7) (Chen et al. 2007), prostratin (10 μM/14h, in peripheral blood lymphocytes, source: *Euphorbia fischeriana* root) (Williams et al. 2004; Tang et al. 2012), myricetin (15 mM/30 min, in human gingival

fibroblasts; sources: e.g. onion, apple, tea, broccoli, red grape) (Gutierrez-Venegas et al. 2013; Scalbert and Williamson 2000), δ toocopherol (10-5 to 10-4 moL/L/72h, in the pancreatic cancer cell lines, HPDE6C7 and HPDE6C7-KRas) (Hussain et al. 2011), EGCG (80 μg/mL/16h, in the human monocyte cell line, THP-1) (Jiagang et al. 2012), folic acid (oral supplementation as 1 mg/Kg/day for five consecutive days per week for four weeks in rats) (Abdalla and Badary 2017) and vitamin D (1,25-dihydroxyvitamin D; $(1,25(OH)_2D_3)$ or 1,24 $(OH)_2D_2$, in murine macrophage cell line, P388D1) (Cohen-Lahav et al. 2006). The mentioned multidirectional relations of the two protein complexes may be crucial during drug specific-anticancer diet creation. Accordingly, the food/plant bioactive compounds and drugs which inhibit NF-kB and/or COX-2, might enhance the anticancerogenic potential of the food/plant bioactive compounds and drugs which inhibit one or some of the cancerogenic proteins, signalings and patways; HIF-1 alpha, MMP9, TNF-α, VEGF, c-Jun, IL-1B, AP-1, Her2+, PI3K/AKT, Notch, Wnt, IL-8 and IL6/STAT-3 (Figure 3).

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THE FOOD BIOACTIVE COMPOUNDS AND CHEMOTHERAPEUTICS FOR THE INHIBITION OF INFLAMMATORY CYTOKINES, IL-8 AND IL-6/STAT3 AND AMELIORATION OF CANCER IN INFLAMMATION ORIGIN

The deregulated overexpression of the multifunctional cytokine, IL-6, and its signal activator, STAT3, are associated with the inhibition of apoptosis, stimulation of angiogenesis, drug resistance and inflammation (Relic et al. 2009; Ji et al. 2012; Guo et al. 2012; Bromberg and Wang 2009). Confirmingly, IL-6 appears as a key cytokine since its inhibition as combined with or without the inhibition of STAT3, has often a much better prognosis, especially in colorectal, breast, skin, liver and brain tumours, chronic myelogenous leukemia and bone metastasis (Waldner et al. 2012; Sun et al. 2014; Lederle et al. 2011; He et al. 2013; Lilja et al. 2001; Reynaud et al. 2011; Ara and Declerck 2010). The cytokine's inducing effect on 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). On the other hand, the following chemotherapeutic agents are the inhibitors of both IL-6 and STAT3. These are; 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), 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) and honokiol (Li et al. 2011). These chemotherapeutics might exhibit greater anticancerogenic and anti-inflammatory effect when they are administered with a a diet which is rich in the following food bioactive compounds which similarly inhibit IL6/STAT3 pathway. These food bioactive compounds are; genistein (10 μM, in synovial fibroblasts) (Relic et al. 2009), kaempferol (10 μM/24h, in HUVECs) (Xiao et al. 2016), baicalein (17 μM/24h, in the human monocytic cell line, THP-1) (Jelic et al. 2016), curcumin (0.25 mmoL/L/24 h, in 3T3-L1 adipocytes) (Chan et al. 2003), beta carotene (5 μM/12h, in the human skin fibroblast cell line, HFP-1) (Obermüller-Jevic et al. 2001), α-tocopherol (150 mg/Kg/d, oral supplementation for 2 weeks in mice with lymphoma, in ascites cells) (Sharma and Vinayak 2011), ascorbic acid (24 mg/min. for 15 min. infusion, in brachial endothelium) (Böhm et al. 2007), I3C (100 μM/24h, in the macrophage cell line, RAW 264.7) (Chang et al. 2011), quercetin (80 μM/30 min., in neutrophiles) (Liu et al. 2005), apigenin (20 μM/2h, in HUVECs) (Wang et al. 2012), EGCG (20 mM/2h, in the human hepatoma cell line, Hep3B) (Madarampalli and Ahmed 2017), arginine (supplementation of L-arginine as 6g/d for 7 days in overweight men aged 46±6 years, with an average body weight of 92.56±9.9 Kg) (Nascimento et al. 2017), amygdalin (12 mg/Kg intraperitoneal injection to mice with acute lung injury) (Zhang et al. 2017), vitamin D_3 (1,25-$(OH)_2D_3$, 800 IU/Kg for 6 weeks in mice with type 1 diabetes) (Labudzynskyi et al. 2016), genistein (50 μmoL/mL/24h, in the human leukemic mast cell, HMC-1) (Kim et al. 2014) and

sulforaphane (40μmoL/L12h, in the prostate cancer cell lines, DU145, LNCaP, PC-3 and CWR22Rv1) (Hahm and Singh 2011).

The inhibition of another cytokine, IL-8, which is responsible for the angiogenesis and antiapoptotic gene expression, has appeared as one of the novel anti-cancer treatments which use IL-8 inhibitors like; reparixin (Leitner 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) and honokiol (Wang et al. 2015). On the other hand, the foods which are rich in the following food bioactive compounds; genistein (40 μM/24h, in the human synoviocyte cell line, MH7A) (Li et al. 2014), L-arginine (2 g/Kg, by gavage in mice for 10 days) (Jeronimo et al. 2016), sulforaphane (5μM/24h, in the human branchial epithelial cell line, BEAS-2B) (Starrett and Blake 2011), I3C (100 μM/48h, in the human T lymphocyte Jurkat cell line (Clone E6-1) (Liu et al. 2017), beta carotene or lutein (20 μmoL/L/2h, in the human gastric carcinoma cell line, AGS) (Kim et al. 2011), apigenin (20 μM/2h, in HUVECs) (Wang et al. 2012), lycopene (2 μM/6h, in macrophages) (Simone et al. 2011), folic acid (70 μg/mL/12h, in the murine-microglia cell line, BV-2) (Cianciulli et al. 2016), quercetin (100 μM/7h, in synovial cells) (Sato et al. 1997), EGCG (160 μM/72h, in the colon adenocarcinoma cell line, Caco-2) (Netsch et al. 2006) and $1,25(OH)_2D_3$ (10^{-8} moL/L/24h, in periodontal ligament cells) (Tang et al. 2013), might enhance the anticancerogenic potential of the chemotherapeutics which inhibit IL-8. Not only these food bioactive compounds and their rich sources which inhibit IL-8, but also the ones which inhibit IL-6/STAT3 pathway, might create a synergism to increase the anticancerogenic potential of both IL-6/STAT3 and IL-8 inhibitors. On the other hand, it may be useful to remind that resveratrol rich nutrition or its supplementation should have been avoided or limited during the treatments with the IL-6/

STAT3/IL-8 inhibiting chemotherapeutics since resveratrol induces the secreation of IL-8 according to the findings of Thiel et al. (2018) (resveratrol, 20 μM/24h, in the human embryonic kidney cell line, HEK293). Their treatment activated the transcription of a chromatin-embedded IL-8 promoter-controlled receptor gene on NF-kB site without any connection with AP-1 binding site. The findings are in accordance with the ones belong to Wendling et al. (2013) who treated the peripheral mononuclear cells with the flavonoid (5μM/48h) and observed the activation of IL-6, only in the patients with both cancer and osteoarthritis. Finally, there is currently a need for the studies which use a cancer cell line to determine the effect of amygdalin, ascorbic acid and tocopherol on IL-6/STAT3.

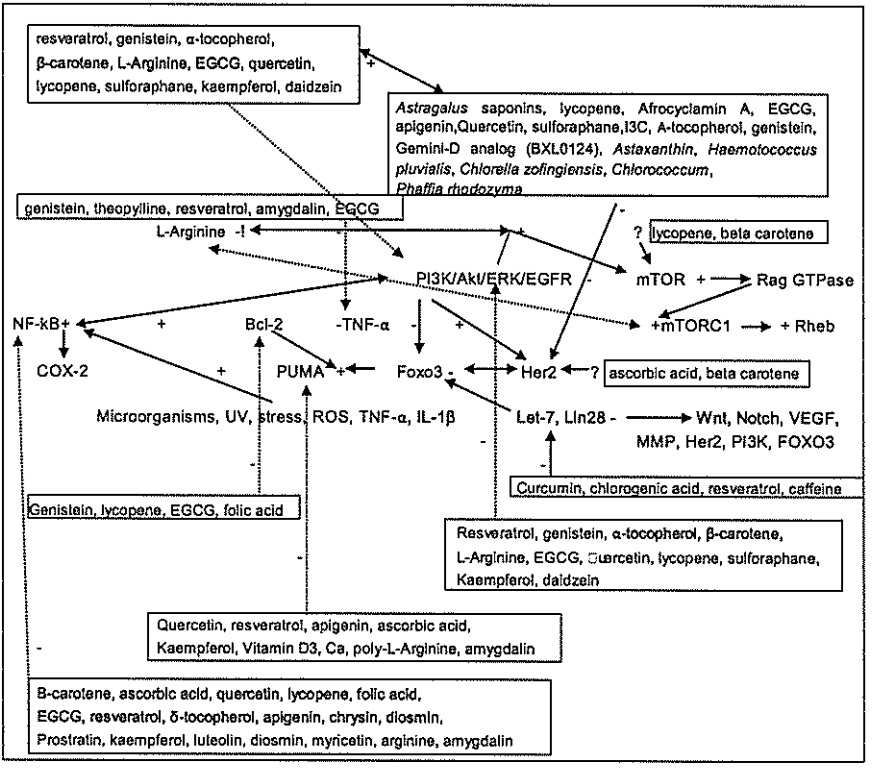


Figure 3. The cancerogenic pathways; PI3K/Akt/ERK/EGFR/NF-kB, Wnt, Notch, Her2, Foxo3, MMP, COX-2, PUMA, Bcl-2, ROS, miRNAs, mTOR and their interactions with food/plant bioactive compounds.

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NOTCH AND WNT SIGNALINGS, THEIR ASSOCIATION WITH FOOD BIOACTIVE COMPOUNDS AND CHEMOTHERAPEUTIC AGENTS

Notch proteins are transmembrane proteins and their interaction with cell-bound ligands establishes an intercellular signaling. The Notch signaling plays a key role in the development of angiogenesis (Liu et al. 2003), expansion of hematopoietic stem cells, the blood cells in the red bone marrow and all 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 apoptosis 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 signaling, Notch inhibitors have currently appeared as a promising novel approach in cancer treatments (Purow 2012; Brennan and Clarke 2013; Aster and Blacklow 2012). The following agents are the namely Notch blockers which are often administered in chemotherapy; 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; Sharma et al. 2015), OMP-21M18 anti-DLL4 mAb (Yan 2011; Couch et al. 2016), 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). Not only the mentioned Notch inhibitors, but also EGCG (20 mg/Kg/28d, in the colorectal cancer cell lines, Lovo, SW480, HT-29 and HCT-8) (Jin 2013), resveratrol (50 μM/24h in the glioma cell lines, A172 and TG8G) (Lin et al. 2011), quercetin (120 μM/48h, in the colon carcinoma cell line, CT-26; in the prostate adenocarcinoma cell line, LNCaP; human prostate cancer cell line, PC3; pheocromocytoma, PC12; Her2+ breast cancer cell line, MCF-7; lymphoblastic leukemia cell line, MOLT-4T; human myeloma, U266B1; human lymphoid Raji cells and ovarian cancer cell line, CHO) (Hashemzaei et al. 2017), delta-tocotrienol 30 μM/72h, and in non small cell lung cancer-NSCLC cell lines, A 549 and H1299) (Ji et al. 2011) and curcumin (90 μM/48h, in the hepatoma cell line, SMMC-7721) (Liu et al. 2014), inhibit the signaling. Therefore, a nutrition which is rich in the food bioactive compounds might have been useful to be able to enhance the anticancerogenic potential of the Notch inhibiting chemotherapeutics by creating a synergy via the inhibition of the signaling. Currently, there is no study about the effect of apigenin, ascorbic acid, amygdalin, L-arginine, lycopene and I3C on the signaling. An important detail according to the latest findings is that three of the bioactive compounds, 1,25 (OH)2 vitamin D3 (10-7-10-9 M/24h, in the leukemic cell line, Kasumi-1) (Karapanagioti et al. 2018), sulforaphane (20 μM/24h, in the prostate cancer cell lines, PC-3 and LNCaP) (Hahm et al. 2012) and folic acid (dipping embryonic neural stem cells, NSCs, in folic acid solution at the concentration of 44 mg/L for 6 days) (Liu et al. 2010) induce the signaling while they increase the ratio of Bcl-2 to Bax. Therefore, it may be a useful approach to avoid or limit the foods which are rich in sulforaphane, vitamin D and folic acid, during the treatments which administer the Notch blockers.

The signaling is most activated in sugar rich consumption (Warburg effect) while the genes involved in the signaling are also effective in glucose uptake, glycolysis, lactate to pyruvate conversion and repression of the tricarboxylic acid cycle (Figure 4). Only a short pulse of Notch activity can elicit the metabolic changes resembling the Warburg effect. PI3K/Akt, the other anti-apoptotic signaling, is stimulated

by the overactivation of Notch (Landor et al. 2011). Especially, the phosphorylation of tyrosine residues recruit adaptor proteins like Grb2 and the p85 subunit of the PI3K complex, which elicit the activation of not only PI3K, but also other anti-apoptotic proteins, e.g. MAPK, Akt, Her2, Notch and Foxo3 (Bublil and Yarden 2007; Maniati et al. 2011; Gopinath et al. 2014; Abravanel et al. 2015; Lindsay et al. 2008; Baker et al. 2014) (Figure 4). On the other hand, membrane-type 1 matrix metalloproteinase (MT1-MMP), a cell surface protease expressed in bone marrow stromal cells, interacts with Notch ligand Delta-like 1 (DII1) and the cleavage of MT1-MMP to DII1 diminishes the Notch signaling (Jin et al. 2011). When the signaling of Wnt is considered, Wnt ligands bind to the Wnt receptors, Frizzled and LRP, which results in nuclear translocation of B-catenin complex of axin. The translocation of the B-catenin inhibits the degradation complex and causes B-catenin accumulation. Additionally, the E6/E6AP protooncogen protein complex stabilizes B-catenin, avoiding its proteasomal degradation and promoting its nuclear translocation. The induced transcriptional activity also triggers the formation of Wnt signaling (Bello et al. 2015; Nusse and Clevers 2017). As a result, the created Wnt signaling activates the Notch signaling and Nrf2 while inhibiting the production of ROS (Cai et al. 2014) and activating the genes of Notch (Jayasena et al. 2008; Andersen et al. 2012) (Figure 4). Briefly, B-catenin, Wnt signaling and Notch/Nrf2 pathway activates each other whereas the activated Notch/Nrf2 pathway inhibits the production rate of ROS. In a nutshell, the inhibitors of B-catenin, Wnt signaling, Notch/Nrf2 and the drugs which induce ROS production are all synergistic with each other. They should be combined with a diet consisting of the foods rich in the food-bioactive compounds which inhibit Wnt, B-catenin, Notch/Nrf2 and induce ROS production. Accordingly, the signaling of 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, Rp-8-Br-cAMP (Voronkov and Krauss 2012), 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) and fulvestrant (Wang et al. 2014), should better be combined with a nutrition which is rich in the following food bioactive compounds which similarly inhibit the Wnt/B-catenin signaling. These food bioactive compounds are; curcumin (30 μM/48h, in medulloblastoma DAOY cells) (He et al. 2014), quercetin (50 μM/24h, in the human teratocarcinoma cell line, NT2/D1) (Mojsin et al. 2014), resveratrol 50 μM/48h, in the colon cancer cell lines, HT29 and RKO) (Hope et al. 2008), apigenin (100 μg/mL/96h, in the osteosarcoma cell lines; U208 and MG63) (Liu et al. 2015), kaempferol (100 μM/24h, in the ovarian cancer cell lines; OVCAR-3 and SKOV-3) (Zhao et al. 2017), isorhamnetin (the methylated form of quercetin) (2μM/24h, in the embryonic kidney cell line; HEK293, in the mouse melanoma cell line; B16F1) (Park et al. 2013), genistein (25 μM/4d, in the renal cancer cell lines; A-498, 786-0, Caki-2) (Hirata et al. 2013), baicalein (5,6,7-trihhdroxyflavone) (200 μM/72h, in the osteosarcoma cell lines; 143B, MG-63) (Dai et al. 2017), EGCG (80 μM/15h, in the human embryonic kidney cell line; HEK293, the human colon adenocarcinoma cell line; SW480, in the human colon carcinoma cell line; HCT116 and Wnt3a-secreting L cells, the cells which secretes growth proteins for embryonic development) (Oh et al. 2014), sulforaphane (5 μM/48h, in the human breast cell lines; MCF7, SUM159 (Li et al. 2010) and lupeol (a novel trieterpene, $C_{30}H_{50}O$) (40 mM/48h, in the colon colorectal cancer cell lines; DLD1, HCT116) (Tarapore et al. 2013). Considering the inhibitory effects on Wnt/β-catenin signaling, the following foods, rich in resveratrol; peanuts, grapes, blueberries and red wine, genistein; currants, raisins, satsumas, Brazil nut, chestnut, coconut, bazelnut and sesame seeds, quercetin and isorhamnetin; onions, kale, broccoli, lettuce, tomatoes, asparagus, red leaf, lettuce and green pepper, apigenin; grapefruit, parsley, onion, orange, tea, wheat sprout, chamomile, EGCG; white tea, green tea and black tea, dark chocolate, fava beans, pears, raspberries, cherries,

blackberries, apples, sulphoraphane; white cabbage, Brussel sprouts, radish, mustard, cauliflower, turnip and Chinese kale, lupeol; white cabbage, pepper, cucumber, tomato, olive, fig, mango, strawberry, red grapes, American ginseng, *Glycyrrhiza glabra* (licorice), soya bean, *Gentiana lutea* (bitter root), carrot (Saleem 2009), genistein; currants, raisins, satsumas, Brazil nut, chestnut, coconut, bazelnut, sesame seeds, baicalein; *Scutellaria baicalensis* and *Scutellaria lateriflora* (Varsha et al. 2017), kaempferol; tea, broccoli, apple, strawberries, beans and curcumin; turmeric and curry, may be advised and useful by creating a synergism to inhibit Wnt/β-catenin signaling with the Wnt/β-catenin inhibitory drugs.

15.a. An unexpected consequence of Notch signaling during the process of antioxidation

Prolonged elevation of ROS causes chronic oxidative stress which leads to sustained induction in the process of antioxidation. The master regulator of the antioxidant response, Nrf2, is induced by oxidative stress and ROS for reducing the oxidative stress in an attempt to eliminate ROS. But, Nrf2 also leads to reductive metabolite formation when it detoxifies ROS. Briefly, the response of Nrf2 to reduce oxidative stress and eliminate ROS, turns into the production of more metabolite formation. Followed by the significant increase in the metabolite formation, the unexpected response of Notch signaling starts to decrease Nrf2 protein levels and express the multiple Nrf2-responsive antioxidants while increasing ROS formation (Kannan and Zweidler-McKay 2015). This also indicates to a possibility of a novel approach by the combined administrations of both Notch and ROS inducers and killing more tumor cells via the formation of more ROS. Furthermore, cytrochrome c influx which induces ROS migration into tumor cells is triggered by Notch followed by Notch's derestoration of mitochondrial membrane potential and Ca^{2+} release (Perumalsamy et al. 2010). Therefore, provided that the anticancer treatment administers the chemotherapeutics which kill cancer cells by producing ROS, though it is ironic, even a hamburger, a creamy dessert or fried potatoes which are high in calorie and harmful in Diabetes, obesity, cardiovascular diseases and disorders and many other metabolic

diseases, may be included in anticancer diet. Hypoxia Inducing Factor (HIF), the gene which contributes to tumor progress through HIF-1α and HIF-2α, has dual effect on Notch. HIF-2α represses the activation of the signaling, in contrast to HIF-1α (Zheng et al. 2008; Hu et al. 2014). On the other hand, the gene expressions of Vascular Endothelial Growth Factor (VEGF) and Notch are induced by Hedgehog signaling (Morrow et al. 2009) while STAT3 is activated by Notch and its effector genes, Hes1 and Hes2 (Kamakura et al. 2004). The effect of MDR on Notch signaling still waits to be highlighted. Under the highlight of the findings, the most important point seems that the Notch inhibiting food/plant bioactive compounds and their rich sources should have been included into the anti-cancer diet as combined during the administrations of each of the inhibitors of Notch, Wnt, hedgehog, VEGF and IL-6/STAT3 since cancer stem cells (CSCs) use all of them to control their self-renewal, embryonic development and differentiation (Yavropoulou et al. 2015).

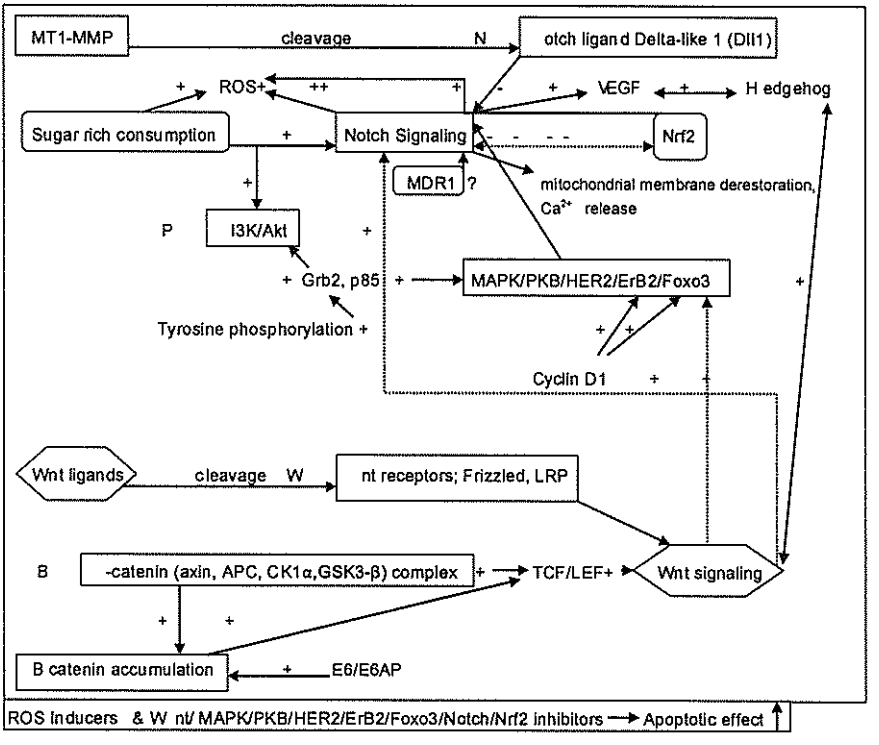


Figure 4. The interactions of the signaling, Notch, with the other signaling and proteins in cancer

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LIN28/LET-7 AND THEIR ASSOCIATION WITH FOOD BIOACTIVE COMPOUNDS

MicroRNAs (miRNAs) are endogenous, small non-coding RNAs. Their main function is gene expression. But, the expression of miRNA is deregulated in human cancer through amplification or deletion of miRNA genes. MiRNAs as tumor suppressors may act as oncogenes due to the deregulation (Peng and Croce 2016). The reduced expression of let-7, one of the tumor suppressor microRNAs, is often associated with cancer and correlates with poor prognosis. On the other hand, two RNA binding proteins (RBPs) and proto-oncogenes, Lin28A and Lin28B, downregulate the let-7 microRNA in many cancers. Lin28A binds the precursor Let-7 by polyuridylating via Terminal Uridylyl Transferase (TUTase) and as a result blocks the microRNA. The subsequent decrease in let-7 expression due to Lin28A leads to overexpression of the oncogenic targets, namely; MYC, RAS, HMGA2 and BLIMP1 (Balzeau et al. 2017). The aberrant expression of Lin28A and/or Lin28B exists in 38% of human colorectal cancer, while neuroblastoma and hepatocellular carcinoma are also reported to have overexpressed Lin28B (Diskin et al. 2012; Nguyen et al. 2014). In the process to inhibit the microRNA, the primary transcript is cleaved by the cytoplasmic Dicer ribonuclease to form mature microRNA. The mature microRNA is incorporated into RNA-induced silencing complex (RISC) which recognizes target mRNAs. The recognition of the target mRNA by the matured microRNA-RISC inhibits the translation of the target microRNA or destabilizes it (HUGO Gene Nomenclature

Committee 2017). The meta-analyses of Ma et al. (2017) from 21 studies involving 3753 cases; HCC (hepatocellular carcinoma), BTCC (bladder transitional cell carcinoma), NSCLC (non-small-cell-lung cancer), BC (breast cancer), CRC (colorectal cancer), GBC (gallbladder carcinoma), LSCC (Laryngeal squamosus cell carcinoma), GBM (glioblastoma multiforme), ESAC (endometrial serous adenocarcinoma) and PDAC (pancreatic ductal adenocarcinoma), have lower Let-7 expressions with worse survival rates (95% CI, 0.52-0.85, 0.66 versus 95% CI, 0.51-0.95, 0.70) (Ma et al. 2017). Similarly, increased expression of Lin28A/Lin28B and/or decreased expression of let-7 in various types of cancer including colon, lung, hepatocellular carcinoma, gastric adenocarcinoma, pancreatic, cervical, ovarian cancers, germ cell tumor, prostate cancer, chronic myeloid leukemia, Burkitt lymphoma, breast cancer, oral squamous cell carcinoma, glioma and melanoma were monitored by King et al. (2011), Pan et al. (2011), Yin et al. (2013), Hu et al. (2014), Torrisani et al. (2009), Li et al. (2011), Dahiya et al. (2008), West et al. (2009), Nadiminty et al. (2012), Viswanathan et al. (2009), Sampson et al. (2007), Malik et al. (2012), Wu et al. (2013), Qin et al. (2014) and Müller and Bosserhoff (2008), respectively. It might be important that, out of the chemotherapeutic agents, sunitinib was determined to inhibit the expression of microRNA-101 (another microRNA like let-7) in advanced renal cell carcinoma (RCC) (Gato et al. 2016). Therefore, the use of sunitinib as combined with let-7 inducers might be contraindicated. Resveratrol (50 μM/24h, in the nasopharyngeal carcinoma cell line, TW01) (Shen et al. 2013), ascorbic acid (via the inhibition of TNF-α)(50 μg/mL, in adipose derived stem cells) (Perez et al. 2013), curcumin (20 μM/4h)(reduced the paclitaxel-induced Lin28 and NF-kB levels, in the hepatic cell line, Hep3B) (Zhou et al. 2015), EGCG (200 μg/mL/96h, in the lung cancer cell lines, NCI-H446 and MSTO-211H) (Zhong et al. 2012), 1α,25-dihydroxyvitamin D_3 (100 nM/48h, in NKT thymocytes) (Pobezinsky et al. 2015), apigenin (20 μM/48h, in the hepatocarcinoma cell line, Huh 7), caffeine (50 μg/mL/48h, in the hepatocarcinoma cell line, Huh 7), curcumin (100 μM748h, in the lung cancer cell line, A549) (Liu et al. 2017), chlorogenic acid (one of the compounds in coffee), procyanidin A2 and B2 (50 μM/mL/48h, in the hepatocarcinoma cell line, Huh 7) (Ohno et al. 2013)

inhibit microRNAs, e.g. miR122, miR185 and miR103. Therefore, the nutrition rich in these bioactive compounds might be useful to enhance the anticancerogenic potential of a limited number of miRNA and Lin28 inhibitors; cisplatin, bortezomib, FAUtpre-let-7g, TUTase inhibitors which block the recruitment 3' terminal uridylyl transferase (TUTase) Zcchc11 (TUT4) and/or Zcchc6 (TUT7) to precursor let-7 RNA to selectively block let-7 biogenesis, the inhibitors whose miRNA and LIN28 inhibiting effects were determined by Sugimura et al. (2012), Tao et al. (2015), McCarty (2012), Lightfoot et al. (2016) and Lin and Gregory (2015), respectively. It might be vitally important to avoid from folic acid since it (100 ng/mL748h) downregulates the expression of let-7 (Mohanty et al. 2016), while there are currently no studies about the effects of kaempferol, alpha-tocopherol, quercetin, I3C, beta-carotene, genistein, lycopene and amygdalin on either LIN28 or let-7. There are currently important findings which indicate to inhibitory effects of miRNAs on some cancerogenic pathways, like miR-129 on Notch (Xiao et al. 2017), Lin28/Let-7 on Wnt and VEGF (Ling et al. 2018), miR-489 on HER2/MAPK (Patel et al. 2016), Let-7 and Lin28 on Bcl-2 (Zhang et al. 2018), Lin-28 on Foxo3 (Lin et al. 2018) and PI3K (Joshi et al. 2016) and Lin28 on IL-6 (Xu et al. 2018). In a nutshell, miRNAs, e.g. Let-7 and Lin28, inhibit many important cancerogenic signaling and genes including Notch, Her2, PI3K, MMP, VEGF, FOXO3, Wnt, Bcl-2 and IL-6., but their overexpression and activation which are often exist in many cancers trigger the same cancerogenic pathways.

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IMMUNOTHERAPY IN CANCER AND ITS ASSOCIATION WITH FOOD/PLANT BIOACTIVE COMPOUNDS. COULD IT BE AN ALTERNATIVE TO CHEMOTHERAPY?

T cell or T lymphocyte is a lymphocyte and a subtype of white blood cell which plays crucial role in cell-mediated immunity. The cell is differentiated from other lymphocyte types, like B cells and natural killer cells, with the existence of T cell receptor on its surface. One of the most significant T-cell receptors in cancer is PD-1, a surface protein receptor. Cancer cells have ability to send a signal to PD-1 by using its ligand, PD-L1, programmed death-ligand, which is a transmembrane protein. Such signal induces the binding of PD-L1 to PD-1 which reduces the proliferation of T cells, limiting apoptosis and inhibiting immune response. The signal also leads to the lower regulation of the signal anti-apoptotic gene, Bcl-2 (Chemnitz et al. 2004). Briefly, there is a close connection and interaction between T cells and PD-1/PD-L1. Once T cells complete their development in the thymus, they enter the bloodstream, reach a lymphoid organ, then return to the bloodstream and recirculate between blood and peripheral lymphoid tissue until they find their specific antigen. Naïve T cells are the cells which have not encountered their antigens. When they reach their specific antigens, they begin to proliferate and form the other type of cells. These cells are capable to the removal of the antigen which is already exist on other cells, especially dentritic cells. These T cells, the armed effector T cells, have an immediate response since they

are capable to remove the antigens and therefore crucial in immune response. Tissue dentritic cells ingest antigen in the infection area, migrate to a local lymphoid tissue and mature there to present antigen to the recirculating T cells. Their surface molecules (co-stimulatory molecules) and major histocompatibility complex (MHC), the cell surface proteins to recognize foreign molecules, differentiate these cells from others and synergize with the antigen to activate the naive T cells (Janeway et al. 2001). All these details reveal the significantly important status of T cells in immune response. On the other hand, a tumor may be PD-L1 negative if it has no T cell infiltrate and a tumor that is unable to express PD-L1 are always PD-L1 negative cancer cells (Ribas and Hu-Lieskovan 2016). The working principle of the treatments of anti-PD-1, PD-L1 and CTLA-4, a protein receptor like PD-1/PD-L1 which downregulates immune response by reducing the proliferation level of T cells, is based on the prevention of the reduction in T cell proliferation followed by the inhibition of PD-1/PD-L1 and CTLA-4 receptors. PD-L1 positive melanoma cancer cells could successfully be inhibited, using a PD-L1 blocking antibody fragment, genetically fused to the extracellular domain of the pro-apoptotic tumoricidal protein, the TNF-related Apoptosis Inducing Ligand, TRAIL (Hendriks et al. 2016). But, one limitation of such treatments is due to the live regulatory T cells, a subpopulation of T cells that maintain tolerance to self-antigens. The live regulatory T cells suppress antitumor immunity, by not using the typicall suppressive factors such as PD-L1 and CDLA-4, but instead, releasing and converting a large amount of ATP to adenosine via CD39 and CD73, the enzymes which convert ADP/ATP to AMP and AMP to adenosine (Antonioli et al. 2013; Mai et al. 2017). So, PD/PD-L1 blockers might not have any significant effect on the regulatory T cells. Another limitation might be the poor response of the tumour cells with lower concentrations of PD-L1 to PD/PD-L1, since the cells which have higher concentrations of these receptors give much more response to the treatments using PD/PD-L1 blockers (Ikebuchi et al. 2014).

CD8 +T cells, which are characterized by a CD8 protein, a transmembrane glycoprotein that serves as a co-receptor for the T cell receptor, binds a histocompatibility complex (MHC) and kills virus/

bacteria-infected or tumour cells. Tumour cells are also capable of limiting the anti-tumor CD8 +T cell responses through their cell surface PD-L1 expression. CD8 +T cells which do not have the expression of CD80 (the protein which is found on dendritic cells) and provide a signal to activate T cells, survive better than activated wild-type CD8 +T cells. This indicates that PD-L1 induces apoptosis in activated CD8 +T cells by signaling through CD80 (Rollins and Johnson 2017). Thus, 'being lacked of CD80', might be a significantly important limitation factor and barrier for immunotherapy in cancer, like the ones mentioned above. Other limitations are the much stronger anti-cancerogenic effect in patients in which pre-existing immunity is suppressed by PD-L1 (Herbst et al. 2014), while a PD-L1 blocker, MPDL3280A, increases the expression of the pro-inflammatory cytokines (IL)-18 and interferon (IFN)-Ƴ (Buchwald and Efstathiou 2015). Briefly, opposite to the recent promising expectations of PD-1/PD-L1 blockers, they can never be defined as the means of immunotherapy which are free of any toxic side effect or limitation. Allthough, there seems a great tendency from chemotherapy to immunotherapy in cancer, it should definitely be taken into consideration significantly that both therapies seem to have their own limitations and side effects. The vaccines which are often claimed to inhibit cancer have the same limitations mentioned above. On the other hand, severe responses with harmful side effects to PD-1/PD-L1 blockers still continue to be exist in such therapies. For example, non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), melanoma, head and neck squamous cell carcinoma (HNSCC), gastric cancer, colorectal cancer (CRC) and pancreatic cancer have 24, 10, 5, 19, 5, 1 and 4% of PD-1/PD-L1 prevalence in 184, 88, 58, 101, 141, 77 and 83 patients, respectively (Herbst et al. 2014).

Pembrolizumab (formerly known as MK-3475), a very high-affinity humanized anti PD-1 IgG4 isotype antibody (2-10 mg/Kg/3w, but with severe side effects and maximum 44% response), pidilizumab (formerly known as CT-011), a humanized anti-PD-1 IgG1 isotype antibody (1.5-6 mg/Kg/2-54w with a higher tolerance and response 64.5 %), nivolumab (formerly known as BMS-936558, ONO-4538 or MDX1106), a human immunoglobulin G4(IgG4)PD-1 immune checkpoint inhibitor

antibody), AMP-224(B7-DC-Ig), a fusion protein between PD-L2 and IgG2a (but exerts its effect by depleting exhausted effector T-cells that express high levels of PD-1 rather than the direct blocking of the PD-1/PD-L1 interaction), MED10680 (AMP-514), BMS-936559 (Human IgG4, S228P), medi-4736 (Engineered human IgG1) and MPDL-3280A (Engineered human IgG1), MSB-0010718C(Avelumab), the PD/PD-L1 blockers whose inhibitory effects on PD/PD-L1 were determined by Guo et al. (2017); Leach et al. (1996); Hamid et al. (2016); Lee et al. (2016); Stewart et al. (2015); Herbst et al. (2014); Buchwald and Efstathiou (2015) and Hassan et al. (2016), may benefit from resveratrol supplementation and/or resveratrol rich nutrition. Resveratrol induces beta-transducin-repeat-containing protein (beta-TRCP), the substrate-recognition subunit of Skp1/Cullin/F-box (SCF) (beta-TRCP) E3 ligases which negatively regulates cell growth and motility of lung cancer cells. On the other hand, the induction of beta-TRCPE3 by resveratrol reduces PD-L1 expression (100 μM/48h, BT549 PD-L1 4NQ mouse breast cancer cell line (Li et al. 2016), which may indicate to a possible synergism of resveratrol rich nutrition and/or supplementation with the mentioned PD/PD-L1 blockers above. Similarly, apigenin (30 μM/30 min, in the mouse MDA-MB-468 human mammary gland cancer cell line) (Coombs et al. 2016), L-argininine (2g/Kg/2w) as combined with αPD-L1 antibody (200 μM/2w and 3 times a week) (He et al. 2017), curcumin (Hayakawa et al. 2014) (as combined with PD-L1 Ab antibody, in human ovarian cancer cell line, OC, but there is no information about neither the doses of the isoflavonoid and the antibody nor their pretreatment intervals) and EGCG (in the mouse non-small human lung cancer cell lines, LC-AI and LU99, though the time for pretreatment with EGCG is informed as 3h, the dose is not published) (Rawangkan et al. 2017), are the food bioactive compounds which may enhance the anticancerogenic potential of PD/PD-L1 blockers via the inhibition of these receptors. Allthough there are many studies as related to ameliorating effect of kaempferol and quercetin on pain, the studied effect mechanisms referred by Kim et al. (2015); De Melo et al. (2009) and Ji et al. (2017), are not performed by searching the PD-1/PD-L1, instead, the other pathways like JNK, NF-kB, Syk (spleen tyrosine kinase) and IRAK4 (IL-1 receptor-associated kinase 4). But the recent

claims which define both isoflavonoids as pain reliever might also be due to their suppressing effects on PD-1/PD-L1 expressions. If this possibility is proven by the studies for cancer treatments, then the nutrition and/or supplementation of both isoflavonoids in anti-cancer nutrition might be useful to enhance both of the suppressing effects of PD-1/PD-L1 blockers and pain relieve via the synergy to maintain a far more inhibition on the mentioned receptors.

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THE ANTI-APOPTOTIC CHAPERONS, GRP78 AND HERP, AND THEIR ASSOCIATIONS WITH FOOD/PLANT BIOACTIVE COMPOUNDS

GRP78, also called as Binding Immunoglobulin Protein, BIP, is a central regulator of endoplasmic reticulum (ER) function because of its protein folding capacity. The chaperon is a 78kDa glucose-regulated protein, which is encoded by HSPA5 gene and it is located in the lumen of the endoplasmic reticulum (ER). The chaperon binds newly synthesized proteins as it is translocated into endoplasmic reticulum. It also 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). GRP78 and its association with various cancers have often been claimed (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). The glucose-regulated protein, GRP78, has been demonstrated to induce proliferation, survival and metastasis. Futhermore, its inhibition sensitizes cancer cells to chemotherapeutic agents, like the increase in sensitivity of colorectal cancer cells to oxaliplatin (Xi et al. 2018). GRP78 regulate the activity of endoplasmic reticulum with another chaperon, Herp. The deficiency of vitamin B_6 causes hyperhomocysteinemia which induces GRP78. Therefore the insufficient intakes of the

vitamin should definitely be avoided particularly during the treatments with GRP78 and Herp inhibitors. The most commonly administered GRP78 and Herp inhibitors currently are; sunitinib (Han et al. 2013), sorafenib (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 (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) and tanespimycin (17-N-allylamino-17-demethoxygeldanamycin, 17-AAg, a derivative of the antibiotic geldanamycin) (Walker et al. 2010). On the other hand, taxol and vinblastine, the two anticancerogenic chemotherapeutic drugs, induce multiple arms of the Endoplasmic Reticulum (ER) stress response, including the up-regulation of GRP78 expression as one of the side effects. But, the treatment with (-)-epigallocatechin gallate (EGCG), synergistically promotes taxol- and vinblastine-induced cell death (EGCG, 10 μM/24h, in the breast cancer cell line, MCF-7) (Wang et al. 2009), by unfolded protein response, making cancer cells more sensitive to both drugs by inhibiting the chaperon. Other GRP78 inhibiting food/plant bioactive compounds are; resveratrol (10 μM/24h, in the human liver cancer cell line, HepG2 (Li et al. 2017), 1,25-(OH)2D3 (1000 nM/24h, in the human umbilical endothelial cells, HUVECs) (Haas et al. 2016), α-Tocopherol succinate (20 μg/mL/24h, in the human gastric cancer cell line, SGC-7901) (Huang et al. 2013), kaempferol (50 μM/24h, in the neuroblastoma cell line, IMR32, and 20 μM/72h, in the human lung bronchial epithelial cell line, BEAS-2B) (Abdullah and Ravanan 2018; Park et al. 2015), ascorbic acid (100 mg/Kg intraperitoneal injection, in testicular cells) (Ji et al. 2012), luteolin, apigenin (20 μM/16h each, in the adrenal gland, phaeochromocytoma cell line, PC12 cells) (Wu et al. 2015) and lycopene (5 μmoL/L/4h, in the neonatal mouse cardiomyocytes) (Xu et al. 2016). A diet rich in these food/plant bioactive compounds might enhance the anticancerogenic potential of the chemotherapeutics which target GRP78 and Herp. The effects of chrysin (5,7-dihydroxyflavone) (sources e.g. propolis,

mushroom) (Kang et al. 2017) is claimed to inhibit the chaperon, while Sun et al. (2011) (chrysin, 40 μM/48h, in the hepatoma cancer cell lines, HepG2 and SMMC-7721) inform the opposite. Therefore, the foods rich in propolis and mushroom should be avoided until the effect of chrysin on the chaperons becomes net and clear. The other food/plant bioactive compounds which should be avoided or limited during GRP78 and Herp inhibitors whose GRP78 or/and Herp inducing effects were determined by the references in the following paranhesis are; sulforaphane (40 μmoL/L/48h, in the hepatocellular carcinoma cell line, HepG2) (Zou et al. 2017), quercetin (150 μM/6h, in the colon cancer cell lines, LS180 and Caco-2) (Natsume et al. 2009), I3C (12 μM/24h, in the breast cancer cell lines, MDA-MB-231 and MCF-7) (Galluzzi et al. 2012), DHA (30 μM/16h in the colon cancer cell lines, HT-29, HCT116 and SW480) (Fasano et al. 2012) and genistein (100 μmoL/L748h, in the human cervical cancer cell line, HeLa) (Yang et al. 2016). These food/plant bioactive compounds and their rich sources might have been contraindicated with the inhibitors of GRP78 and Herp since they induce the expression of the chaperons. But, if the chemotherapy is based on the administration of GRP78 and Herp inducers, then the same food/plant bioactive compounds and their rich consumptions might have been useful by creating a synergism to induce the chaperons. These chemotherapeutic agents which induce GRP78 and/or Herp are; 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), STF-083010 (a small-molecule inhibitor of Ire1, a serine/threonine-protein kinase) (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 which causes apoptosis) (Carew et al. 2013) and thapsigargin which targets peptide containing aspartic acid with antineoplastic activity (Krige et al. 2008). The status of folic acid is ambiguous and critic. Currently, there is no study about the effect of the vitamin on the chaperon. On the other hand, cancer cells and also healthy ones have folic acid receptors. After the determination of its effect on the chaperons and if the effects are inhibitory, then the

loading of the vitamin into nanoparticules which target cancer cells may be a much easier process because of the folic acid receptors which are exist in every cell. A similar method has already been performed by Zhao et al. (2015). The bovine serum albumin (BSA) nano particules which are conjugated with the monoclonal antibody and the anticancer drug (5-fluorouracil) against GRP78 (mAbGRP78), could be transferred specifically to the hepatocellular carcinoma cell line, SMMC-7721, in which GRP78 is overexpressed. The method inhibited the adhesion, invasion and metastasis of the hepatocellular carcinoma cells. The method of Zhao et al. (2015) may be modified and upgraded by loading any of the food/plant bioactive compounds like apigenin or quercetin by using nanoparticules and folic acid receptors.

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P21CDKN1A AND P27 IN CANCER AND THEIR ASSOCIATION WITH FOOD/ PLANT BIOACTIVE COMPOUNDS

p21CDKN1A is a potent inhibitor of cyclin-dependent kinases (CDKs), a family of protein serine/threonine kinases, which are needed to drive each of the major cell cycle transition points (G1, S, G2, M), cell growth, DNA replication and mitosis. The endogenous p21 prevents genomic instability which is caused by deregulation in the DNA polymerase activity during genomic DNA synthesis, while the depletion of p21 slows down nascent DNA elongation, triggers permanent replication defects and promotes the instability of hard-to-replicate genomic regions (Mansilla et al. 2016). P21CDKN1A is able to stimulate the PARP-1 (DNA nick-sensor poly ADP-ribose polymerase-1) binding to base excision repair (BER, the DNA repair intermediates) (Dutto et al. 2016). On the other hand, cancer is caused by genetic changes followed by the failure to accurately replicate the DNA. p21CDKN1A makes the inhibition on CDK by both binding PARP-1 to BER and inhibit the binding of DNA polymerase delta at the G1/S phase transition. But, although it may inhibit cell cycle, the methylation of p21 at arginine 156 and promoted phosphorylation of threonine 145 on p21 results in the increase of cytoplasmic localization of the enzyme. The cytoplasmic presence of p21 makes cancer cells more resistant to cytotoxic agents (Nakakida et al. 2015). This ability gains a critical status to p21 during chemotherapy and immunotherapy in cancer. In a nutshell, p21CDKN1A has dual effect (Stivala et al. 2012), like in many other crucial genes in

cancer. So, the dual effect of the gene requires oncologist and clinic nutritionist to be vigilant and cautious by concerning its apoptotic effect by inhibiting CDK, but also its cancerogenic effect by protecting cancerous cells against the cytotoxic effect of chemotherapeutic agent. When the association of p21 with chemotherapeutic agent is considered, doxorubicin causes DNA damage which knockdowns p21, while increasing p53 upregulation in HT1080 fibrosarcoma cells (Broude et al. 2007). On the other hand, the effect of all anti-cancer drugs on p21 is not the same. Opposite to doxorubicin, sunitinib increases expression levels of both p21 and p53 in renal cell carcinoma (Panka et al. 2013). Histone deacetylases (HDACs) play an important role in the gene's expression by catalyzing the removal of acetyl groups from histones. This deacetylation causes chromatin condensation and repression of the transcriptions of tumor suppressor genes (Bolden et al. 2006). Therefore, the administration of the HDAC inhibitors; hydroxamic acids (vorinostat and panobinostat), short-chain fatty acids (valproic acid and pivanex), benzamides (MS-275 and CI-994) and cyclic tetrapeptides (desipeptide), has appeared as a novel approach in anti-cancer treatments by protecting tumor suppressors from the mentioned transcriptional repression while increasing p21 levels and inducing CDKN1A (Zhang et al. 2003; Farhat and Houhou 2013). Presently, vorinostat (Uehara et al. 2012), panobinostat (Cheng et al. 2018), bortezomib, docetaxel, combination of bortezomib and docetaxel (Canfield et al. 2006), and the combination of vorinostat and capecitabine with cisplatin (Yoo 2016), have gained a wide administration platform in chemotherapy by activating the enzyme. Similarly, some of the food/plant bioactive compounds in the last few decades have also been claimed to increase the expression of the enzyme. These are; kaempferol (80 μM/24h, in the ovarian cancer cell lines; OVCAR-3 and A2780/CP70, while inhibiting VEGF expression and inducing ERK/NF-kB pathway) (Luo et al. 2012), quercetin (50 μM/72h, in the human hepatoma cell line, HepG2) (Mu et al. 2007), I3C (5 mg/Kg/2w, in the mouse estrogen receptor-positive cell line, MCF-7 and the triple-negative breast cancer cell line, MDA-MB-231) (De Santi et al. 2011), apigenin (10 μM/24h, in the human colorectal cancer cell line, HCT 116) (Zhong et al. 2010), genistein, biochanin-A (100 μM/3d, in the non-tumorigenic human mammary gland cell line, MCF-10A,

and the human breast adenocarcinoma cell line, MDA-MB-231) (Seo et al. 2011), resveratrol (100μM/L/48h, in the human lung carcinoma cell line, A549 while increasing p53 levels) (Yuan et al. 2015), beta carotene (4μM/72h, in the human mammary cancer cell line, MCF-7) (Palozza et al. 2004), lycopene (75 μM/5d, in the breast cancer cell lines; MCF-7, SK-BR-3 and MDA-MB-468) (Takeshima et al. 2014), EGCG (50 μM/36h, in the musculus mammary gland tumor cells, while reducing the level of PCNA) (Dickinson et al. 2014), calcitriol (0.05 μg/24h) and 1,25-dihydroxy-16-ene-23-yne vitamin D(3)(16,23-D(3) (0.5 μg/24h) (in mice retinoblastoma cells) (Audo et al. 2003) and folic acid (10μM/21h, in the human umbilical vein endothelial cells, HUVECs and 50 μM/24h, in human epidermal keratinocytes) (Chew et al. 2012; Hou et al. 2013). The nutrition which is rich in the food/plant bioactive compounds might enhance the anti-cancerogenic potential of the chemotherapeutics above by creating a synergy via the activation of the enzyme.

p27 (kip 1), a member of the inhibitory cdk proteins, coordinates the activation of cyclin E-cdk2. E-cd2, the kinase partner of E cyclins which drive tumor cell proliferation. It's activation with the accumulation of cyclin D-cdk4, the kinase that regulates the G1-S checkpoint, leads to proliferation as a response to antimitogenic signals (Geng et al. 2018; Blain et al. 2003; Hamilton and Infante 2018). On the other hand, p27 causes apoptosis by inhibiting cdk4/6 (Blain 2018). Like p27, there are currently some of the cyclin-dependent kinase (CDK) inhibitors which target D-cdk 4/6 while increasing the expression level of p27. These are; palbociclib (in mantle cell lymphoma-MCL, myeloma, breast, lung, brain and colon cancer), ribociclib (in breast cancer, MCL, malignant rhabdoid, tumor-MRT, liposarcoma, melanoma, neuroblastoma), combination of ribociclib and abemaciclib (in acute myeloid leukemia-AML, non-small cell lung carcinoma-NSCLC, glioblastoma, colorectal and lung cancer) and abemaciclib (in AML, NSCLC, glioblastoma, colorectal and lung cancer) (Hamilton and Infante 2016). AP-1, the activating-1 transcription factor which transduces growth signals through signal transduction pathways to nucleus, and the members of the transcription factor namely c-Fos, lead to the expression of genes which are involved in malignant transformation of cells (Shen et al.

2008). In the early stages of G1, p27 inhibits the activity of AP-1 through the down-regulation of its cofactor, JAB1 (Coqueret 2003). Therefore, it might be a smart and more effective approach to combine the inhibitors of AP-1 and the inducers of p27, namely; MeOH and SSA (Satoh and Kaida 2016), particulary in the early phases of cancer. Such combination of the p27 inducers; MeOH, SSA, palbociclib, ribociclib and abemaciclib with a very limited number of AP-1 inhibitors (whose AP-1 inhibitory effects are determined by the authors and their studies in the following paranthesis); SR 11302 (Mishra and Kim 2017; Gonzales-Rubio et al. 2016), SP100030 (also inhibits NF-kB) (Ye et al. 2015), SP600125 and c-Jun (Farmaki et al. 2016), might have more intense anticancerogenic effect by creating a synergism for a much greater inhibition on cdk4/6 and activation on p27. On the other hand, quercetin (25 μM/72h, in the HepG2 cells), silibinin (milk thistle) (75μg/mL/72h, in the human colon cancer cell line, HCT116) (Hogan et al. 2007), lycopene (10 μM/72h in the colon-colorectal adenocarcinoma cell line, HT-29) (Tang et al. 2008), sulforaphane (90μM/72h, in the breast cancer cell line, MCF7-GFP) (Azarenko et al. 2008), curcumin (40 μM/24h, in the pancreas cancer cell line, Panc-1) (Zhao et al. 2015), tangeretin (a polymethoxylated in the peel of citrus fruits, 50μM/48h, in the pituitary adenoma cell line, AtT20) (Pan et al. 2002), and beta carotene (20 μM/96h, in the pituitary adenoma cell line, AtT20) (Haddad et al. 2013) and the foods rich in these flavonoids, should be included into diet during the administration of the AP-1 inhibitors and p27 activators. Because these food bioactive compounds inhibit AP-1 and activate p27 and might enhance the anti-cancerogenic potential by creating a synergism with the AP-1 inhibitors and p27 inducers through the inhibition of AP-1 and activation of p27. Cliché diet recommendations like 'fat limitation or elimination from the diet' should definitely be avoided, except for the patients with a cardio-vascular disease or disorder, since the recent findings claim that a high fat diet induces the cell cycle inhibitors, p27 (Kip1) and p21 (Cip1)(Wu et al. 2015; Diez-Juan and Andres 2001; Khanna 2009).

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ANOTHER GOOD EXAMPLE FOR THE INVALIDITY OF THE CLICHÉ NUTRITION RECOMMENDATIONS, P38, AND ITS ASSOCIATION WITH FOOD/ PLANT BIOACTIVE COMPOUNDS

The p38 MAPkinases, as one of the main subgroups of the family, Mitogen Activated Protein Kinases (MAPKs), the enzymes which mediate a wide range of functions in response to extracellular stimuli, have often been crucial in both cell proliferation and cell death. The activation of p38 MAPKs (p38-MAPKα, p38-MAPKβ, p38-MAPKϒ, and p38-MAPKδ) leads to the mesenchymal transition of cells in tumor, and invasion and migrating capabilities of cancer cells (Koul et al. 2013). The activation of p38 MAPKs is formed through phosphorylating threonine and/or tyrosine residues in the activation loop, allowing substrates access to the catalytic residues, e.g. Lys53 and Asp168 in p38α. The phosphorylation on the threonine residue is the essential one in the activation. Another important factor which contributes to the cancerogenic potential of the enzyme is its nuclear translocation. The MAPKs, p38 and JNK, bind to heterodimers, importin 3, 7 and 9. A myristocylated peptide called Perry specifically blocks the binding of p38 and JNK to importins and restricts their nuclear translocation. This interruption in binding of p38 to nucleus importins has been informed to inhibit the progress in colon cancer (Flores et al. 2019). In contrast, the same enzymes may induce DNA damage, arrest cell cycle and may

cause apoptosis if they are over-activated (Eom and Choi 2010). Because of the dual effect of p38MAPKs in cancer, either their inhibition or activation, has often been a target in anti-cancer treatments. 2-(3-methyl-thiophen-2-yl)-4-(3,4-dioxybenzene)thiazole (a small molecule) (Li et al. 2014); MMC (Mitomycin C), CDDP (cis-diamminedichloroplatinum), TG (Thioguanine) (Xi et al. 2015), nocodazole, vincristine, vinblastine, taxol (Olson and Hallahan 2004), paclitaxel (Reshkin et al. 2012), sunitinib (Dufies et al. 2017), sorafenib (Cervello et al. 2012), thapsigargin (Kim et al. 2010), cisplatin (Hernandez Losa et al. 2003), nicotinamide (an NAD+ and NADP+ coenzyme precursor (Sun et al. 2008), cannabidiol (a phytocannabinoid derived from cannabis species with analgesic, anti-inflammatory, antineoplastic and chemopreventive actions (Hwang et al. 2017), are the p38 inducing drugs which are currently being used in chemotherapy. The food bioactive compounds which similarly induce p38, with their treatment durations and concentrations are; apigenin (20 μM/48h, in the melanoma cells, B16) (Ye et al. 2011), folic acid (70 μg/mL/24h, in the microglial cells, BV-2) (Cianciulli et al. 2016), vitamin E succinate (20μM/48h, in the human prostate carcinoma cell line, PC-3) (Shim and Eling 2008), EGCG (100 μM/72h, in human placental choriocarcinoma cells) (Shih et al. 2016), ascorbic acid (500 μM/5d, in the murine melanoma cell line, B16F10) (Lee et al. 2011), quercetin (200 μM/6h, in the breast cancer cell line, MCF-7) (Lee et al. 2010) and sulforaphane (20 μM/24h, in the human bladder cancer cell line, T24) (Shan et al. 2009). On the other hand, p38 is inhibited by honokiol (Lee et al. 2017), SB203580 (Su et al. 2010), doramapimod (BIRB796) (Moon et al. 2015), SB202190 (FHPI) (Chen and Stinski 2002), ralimetinib (LY2228820) (Patnaik et al. 2016), VX-702 (Damjanov et al. 2009), PH-797804 (MacNee et al. 2013), VX-745 (Duffy et al. 2011), AMG-548 (Verkaar et al. 2011), pamapimod (Hill et al. 2008), SB239063 (Underwood et al. 2000), Skepinon (Taves et al. 2016), rationale, Losmapimod (O'Donoghue et al. 2015), asiatic acid (Huo et al. 2016), BMS-582949 (Emami et al. 2015), pexmetinib (Bachegowda et al. 2016), JX-401 (a potent non-cytotoxic cell membrane permeable p38α inhibitor)(Friedmann et al. 2006), SD-169 (Yang et al. 2012), LLZ1640-2 (an antibiotic)(Gunnell et al. 2010), SB202190 (Hirosawa et al. 2009), LY2228820 (Tate et al. 2013), CMPD1 (the

inhibitor of tubulin, a protein family which forms microtubules) (Gurgis et al. 2015), PD169316 (Fu et al. 2003), RWJ6765 (Antoon et al. 2012), SB202190 hydrochloride (Huang et al. 2004), CGH2466 (Trifilieff et al. 2005), VX702 (Damjanov et al. 2009), TAK715 (also the inhibitor of Wnt/β-catenin pathway) (Verkaar et al. 2011), VX745 (Duffy et al. 2011) and SKF-86002 (Asaduzzaman et al. 2008). When the effect of food bioactive compounds on p38 inhibition is concerned, the following ones; lycopene (30μM/96h, in the human colorectal cancer cell line, SW-480) (Cha et al. 2017), kaempferol (100 μM/72h, in the renal cell carcinoma cell line, RCC) (Song et al. 2014), arginine (2 mmol/L) and glutamine (10 mmol/L) (in patients with Crohn's disease) (Lecleire et al. 2008), genistein (5 mg/Kg/30d via intragastric injection in rats) (Ganai et al. 2015), 1,25-dihydroxyvitamin-D3 (50 nmol/L/24h, in the prostate cancer cell lines, LNCaP, PC-3 and DU145) (Nonn et al. 2006) and beta-carotene (20 μM/2h, in the human gastric epithelial cell line, AGS) (Jang et al. 2009), were informed to inhibit p38 MAPKs. The status of nicotinamide among the p38 activators is the one, having the most unusual effect in the field of anti-cancer nutrition. The reduction of NF-kB1, the nuclear factor kB, which belongs to a family of transcription factors and whose aberrant or constitutive activation has been detected in human malignancies (Dolcet et al. 2005), results in increased phagocytosis of tumour cells by macrophages with a reduction in a tumour volume (Betancur et al. 2017). While there is a close relation between phagocytosis and the decrease in tumour volume, the phagocytosis is highly dependent upon the activation of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (Nox). Ironically, the activation of Nox as the main source of ROS production and a poor diet from antioxidants stimulate phagocytosis as opposite to antioxidants and the treatments that administer Nox inhibitors. Nox-derived ROS up-regulate both PI3K and p38 MAPKs (Sun et al. 2008) which may also results in apoptosis. The findings clearly indicate that the current status of anti-cancer nutrition is at the edge of a weird corner. ROS, the reactive oxygen species, which are blamed for various diseases and disorders from stroke to atherosclerosis and diabet can induce phagocytosis against tumour cells and be apoptotic. The necessity to recommend an anti-cancer diet with its rich antioxidant content, low

carbohydrate and lipid profile, should carefully be scrutinized once more.! Such reevaluation about the lipid and carbohydrate rich foods as the main ROS sources would not mean that these foods would necessarily be beneficial and free from any risk in healthy nutrition. Only, the current findings clearly reveal that whether the food is good or bad in a disease, particularly in cancer, depends on the type of the 'approach in anti-cancer treatment' and the 'drug'. When the up-regulation of PI3K with the activations of p38 and ROS and the increase in apoptosis through their synergism followed by their activations are concerned, then the combination of the p38 inducing drugs, namely, 2-(3-methyl-thiophen-2-yl)-4-(3,4-dioxybenzene) thiazole, MMC, CDDP., as combined with the following Nox inhibitors, e.g., apocynin (a naturally occurring organic compound, originally a medicinal plant herb which is derived from the root of Canadian hemp (*Apocynum cannabinum*) and *Picrorhiza kurroa*), honokiol, plumbagin, Gp91ds-tat (a peptide, which can inhibit the oxygen radical production), serine protease inhibitors (4-(2-aminoethyl)-benzenesulfonyl fluoride), phenylarsine oxide, gliotoxin, ebselen, VAS2870 and HMGCoA reductase inhibitors (statins) (Kim et al. 2017), with the ROS and Nox inducing drugs, may be a smart approach. Because, such approach may yield a synergism to increase in the activations of p38 and ROS to a stronger apoptosis. Unexpectedly and paradoxically, even a fat and sugar rich diet may be beneficial during the administrations of the Nox and p38 activating drugs since the activations of both p38 and Nox as combined with a 'sugar and fat rich diet', may be synergistic to generate ROS more and target cancer cells with a much greater amount of ROS's. The same approach may also be useful during the combined administrations of p38 or/and Nox activating drugs with the ROS producing drugs namely, sunitinib, sorafenib, tetrandrine and cisplatin. In contrast, the following Nox inhibitory food bioactive compounds with their determined concentrations to inhibit Nox; decaffeinated green tea extract (2.5 μg/mL/72h in HeLa cells) (Morre et al. 2003), folate (12 nmol/L serum concentration) (Holven et al. 2002), sulforaphane (0.25 mg/Kg/d for 4 weeks in rabbit)(Shehatou and Suddek 2016) and quercetin (1 mg/Kg/5months in rabbit)(Wan et al. 2009), may be contraindicated due to their inhibiting effect on p38 MAPK activity and Nox, during the

treatments with the mentioned ROS and Nox inducers. When the effect of I3C is analysed, its status in p38 activity is still unclear and needs to be highlighted since the findings of Safa et al. (2017) claim its triggering effect on p38, while Ping et al. (2011) inform the opposite.

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THE ERRORS IN MISMATCH (MMR) PROTEINS AND THE EFFECTS OF SOME OF THE FOOD/PLANT BIOACTIVE COMPOUNDS ON THE ERRORS AND MMR PROTEINS

MMR proteins or the mismatch repair genes, the nuclear enzymes, play essential role in the repair of base to base mismatch that occur during DNA replication in cell proliferation. They bind to these abnormal DNA areas and remove them by forming complexes and heterodimers. Ironically, their increase can cause a number of DNA replication errors, especially in the areas of the genomes which have short repetitive nucleotide sequences. The errors in the short repetitive nucleotide sequences are called as microsatellite instability (MSI). The genes that encode proteins in the MMR system are; MSH2, MSH3, MSH6, MLH1, PMS1, and PMS2 (Kheirelseid et al. 2013). The loss in one of these proteins may lead to a higher risk of cancer formation, like in the 18 patients out of 19 with a family history of colorectal, endometrial, ovarian and stomach cancer (Long et al. 2014). On the other hand, there is no such association in small-cell lung cancer cells, which may be due to inactivation of a second pathway that leads to MMR deficiency in small cell lung cancer (Hansen et al. 2003). Opposite to small-cell lung cancer, a significant association for non-small cell lung cancer (Li et al. 2013), also non melanoma skin cancer (Young et al. 2008) and colorectal cancer (Devaud and Gallinger 2013) were detected. Presently, there is no study which clearly highlights the association of the genes with brain tumors. The damage mutation or loss of MMR genes decreases the

efficiency of repair of DNA lesions caused by free radicals and oxidation. Confirmingly, MSH2-deficient cells have more oxidative damage (8-oxoG and thymine glycol) when exposed to radiation (DeWeese et al. 1998). The same positive correlation between the oxidative DNA damage and the higher inactivity level in DNA mismatch repair system has also been informed by Bridge et al. (2014). The findings of Ding et al. (2016) seem to have uppermost importance, indicating that the mismatch repair (MMR) protein heterodimer, MSH2-MSH6, participates in the oxidative damage-induced recruitment of DNA methyltransferase 1 (DNMT1) to chromatin, reducing transcription and preventing from interfering with the repair process. These findings may reveal a possible synergy between the anti-cancer drugs which kill cancer cells by producing reactive oxygen species (ROS) and the anticancer drugs which kill cancer cells by inhibiting MMR proteins, while indicating to superior and more beneficial effects of their combined administrations. Like the dual effect of the ROS, 'the promoting effect on disease and aging', but also 'being anticancerogenic', any inhibition on MMR proteins if combined with ROS-inducing chemotherapeutics, might also be in anticancerogenic effect. Such combinations might prevent the DNA of tumor cell from the repair process of MMR genes, while ROS influx could kill these defected cells much easier. Therefore, as a part of a very novel anti-cancer approach, the mismatch repair (MMR) chemical blockers; 9,10-Bis (aminoalkoxy) anthracenes, cyclopentnaphthoquinone and cyclopentanthraquinone derivatives, C12N15/85, O^6benzylguanine, O^6-(4 bromothenyl) guanine, methoxyamine and lucanthone (both of which are the inhibitors of APE, a multifunctional protein which possesses DNA repair and transcriptional activity), oleanolicacid, edgeworin, botulinic, stigmasterol, NCS-666715 and NSC-124854 (the inhibitors of Pol β, polymerase beta which conducts gap filling DNA synthesis in base-excision repair), hydroxyurea-based FEN1 inhibitors (the inhibitors of FEN1, flap endonuclease 1, which is overexpressed in lung cancer, while its suppression results in decreased DNA replication), iniparib, olaparib, ABT-888, AZD2461, BMN673, E7449, INO-1001, CEP-9722, MK-4827, rucaparib, velaparib, PJ-34 and DPQ (the inhibitors of PARP1i polyADP-ribose polymerases, cell signaling enzymes which are involved in poly ADP-ribosylation of DNA-binding proteins) (Sharma et

al. 2009; He et al. 2017 and Kelley et al. 2014), might yield a far stronger anticancerogenic potential, if they are administered as combined with the anti-cancer drugs which target cancer cells by producing ROS, namely; costunolide, mitomycin c, and cisplatin. Such combination might yield a much more significant anti-cancerogenic affect by forming a synergism which is based on the combined effect of ROS induction and MMR protein inhibition. On the other hand, kaempferol (Wu et al. 2015, but the dose and time for the human promyelocytic leukemia HL-60 cells, not reported!), EGCG, lycopene, ascorbic acid, α-tocopherol (with 50 μM/14d, 20μM/14d 600μM/14d 100 μM/14d dose and time combinations respectively, in the human colorectal cancer cell line, HCT 116) (Mure and Rossman 2001), resveratrol (250 μM/48h, in the pancreatic cancer cell lines; AsPC-1, BxPC-3, MIAPaCa-2 and Panc-1, and, in the breast cancer cell line, MCF-7) (Nauman et al. 2017; Leon-Galicia et al. 2013), quercetin (100μM/36h, in the cervical cancer cell line, HeLa-MR) (Christman et al. 2002) rich nutrition/supplementation, have the same inhibitory effect on MMR proteins. So, they might enhance the anticancer potential of the MMR blockers by forming a synergy to make a much greater inhibitory effect on the proteins. But, arginine rich food nutrition should better be limited, since it methylates Rad9 (a DNA repair protein) and regulates its function (He et al. 2011) and therefore, it might be contraindicated with the anticancer therapies which target MMR proteins.

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ABC PROTEINS, P-GP, S1P, THEIR RELATION WITH CANCER NUTRITION

Sphingosine (2-amino-4-trans-octadecene, 1,3-diol) (C18H37NO2), is an 18-carbon amino alcohol with an unsaturated hydrocarbon chain which forms a primary part of sphingolipid. The bioactive lipid, sphingosine 1-phosphate (S1P) is produced by phosphorylation of sphingosine. S1P which is formed by sphingosine kinase 1 (SK1) at the plasma membrane is released from cells via S1P transporters to act on S1P receptors to promote tumorigenesis (Pyne et al. 2018). S1P, the pleiotropic and bioactive lipid mediator, regulates proliferation, survival, angiogenesis/lymphangiogenesis and immune responses. The close relation between S1P, ABCC1 and MRP1 has also a significant role in the progress of tumorigenesis. ATP-binding cassette (ABC) transporters are membrane-bound proteins which may contribute to the resistance of tumor cells to a number of drugs including chemotherapeutics. ABCC1 is the gene from the ABC transporter family to the Multidrug Resistance associated Protein 1 (MRP1) (Kunicka and Soucek 2014). The latest findings reveal that MRP1 acts as the transporter for S1P efflux from the endothelial cells while deletion of MRP1 terminates endogenous signaling to Sphingosine 1 Phosphate-Receptor 1 (SPR1) (Cartwright et al. 2013). So, the novel targets in anti-cancer treatments, the inhibitions of ABCC1, MRP1 and SP, may be an important criteria to consider in the creation of an anti-cancer diet during the treatments with the inhibitors of ABCC1, MRP1 and S1P. The following chemotherapeutic agents are the ABCC1 inhibitors. These are; MK-571

(an important note about the agent is that the knockdown of ABCC3 by MK-571 also enhances doxorubicin retention in breast cancer cells) (Balaji et al. 2016), reversan (Cho et al. 2011), nucleoside, nucleotide and non-nucleoside reverse transcriptase inhibitors, tenofovir, delavirdine, efavirenz, emtricitabine (Weiss et al. 2007), vandetanib (Zheng et al. 2009), 3B-acetyl tormentic acid (the acid reverts MRP1/ABCC1 mediated cancer resistance through modulation of intracellular levels of intracellular glutathione, GSH) (Rocha et al. 2014), indolopyrimiidine derivatives (e.g. gefitinib) (Nakamura et al. 2005), pyrrolopyrimidine derivatives (Schmitt et al. 2016), indomethacin (the nonsteroidal anti-inflammatory drug also overcomes doxorubicin resistance by inhibiting MRP1/ABCC1) (Matsunaga et al. 2006), B-cholanic acid, e.g. deoxycholic acid and urso-cholanic acid, both of which are the novel ABCC1 inhibitors) (Chewchuk et al. 2018), lignans, e.g. mataresinol, conidendrin, 7-oxomatairesinol, 7-hydroxy-secoisolariciresinol, 7-hydroxymateiresinol, pinoresinol (from Norway spruce, *Picea abies*), conidendrin, 4,4'-dihydroxy-enterolactone and schizandrins, e.g. schisandrin A, B (Wrobel et al. 2010). The most currently administered MDR-1 inhibitors in chemotherapy are; zosuquidar trihydrochloride, voruciclib (important note that voruciclib significantly potentiates the effect of paclitaxel and doxorubicin) (Gupta et al. 2018), tryptanthrin (Yu et al. 2007), celecoxib (Roy et al. 2009), itraconazole, a P-glycoprotein pyrimethamine (Wang et al. 2017), niguldipine hydrochloride (a selective α 1-adrenoceptor, a G-protein-coupled receptor that is target of many catecholamines like norepinephrine (noradrenalline) and epinephrine (adrenaline) and dexniguldipine-HCL (Hofmann et al. 1995). The inhibition of MDR-1 or ABC transporters may be a sole approach in anticancer treatments, but the close relation among MDR-1, ABC transporters and P-glycoprotein remark a significant importance of the combined inhibitions of them to a better prognose. Especially, P-glycoprotein (P-gp), the protein from the family of ABC transporters which functions in cellular detoxification by pumping a widé range of xenobiotic compounds out of the cell, should have been concerned as the main pivot in the anticancer treatments which administer the inhibitors of MDR or ABC transporters. The inhibition of P-gp directly increases the sensitivity to drug by inhibiting both MDR and the activity

of ABC transporters. Therefore, the involvement of the food bioactive compounds with their inhibitory effect on ABC/MDR/P-gp pathway into the anticancer diet, which might be in synergism with the chemotherapeutic agents which inhibit ABC/MDR/P-gp, may improve the prognose. Accordingly, the most commonly administered P-gp inhibitors are; the first-generation inhibitors, e.g. verapamil, nifedipin, cyclosporine A, ibuprofen, reserpine, tamoxifen amiodarone, the second-generation inhibitors, e.g. valspodar, dexverapamil, MM36, cinchonine and quinine homodimer Q2 and the third generation inhibitors, e.g. tariquidar (XR9576), zosuquidar (LY335979), elacridar (GF120918) and PGP4008 (Yu et al. 2016). The mentioned P-gp, MDR and ABC inhibitors above might benefit from the following food bioactive compounds via the synergism to inhibit the pathway of P-gp/ MDR-1/ABC. These are; icaritine (isolated from *Herba epimedium*, 30 μM/4h, in the human hepatocellular carcinoma cell line, HepG2) (Sun et al. 2013), EGCG (100 μg/mL/72h, in the breast carcinoma cell line, MCF-7, an important note is that EGCG also increases the sensitivity to tamoxifen by inhibiting Pg-p) (Farabegoli et al. 2010), biochanin A, silymarin (150 μM/12 d each, in the colon colorectal cancer cell line, Caco-2) (Zhang and Morris 2003), genistein (200 μM/1h, in the human breast cancer cell line, MCF-7) (Castro and Altenberg 1997), kaempferol (200 μM/24h, in the human cervical carcinoma cell line, KB-V1) (Limtrakul et al. 2005), quercetin (25μM/24h, in the colorectal cancer cell line, Caco-2) (Bhutto et al. 2018), apigenin (100 μM/60 min, in gut sac cells, important note is that the flavonoid increases the sensitivity to paclitaxel) (Kumar et al. 2015), procyanidin (200 μM/48h, in the human ovarian cancer cell line, A2780/T) (Zhao et al. 2013), myricetin (100 μM/48h, in the ovarian cancer cell line, OVCAR 3) (Zheng et al. 2017), wogonin (30 μmol/L/24h, in the human leukemia cell line, HL-60) (Lee et al. 2009), resveratrol (100 μM/4h, in canish renal cells) (Li et al. 2016), coumarin (50 μM/72h, in the multi-drug resistant breast cancer cell line, MCR-7/ADR) (important note about the flavonoid is that it increases the sensitivity to paclitaxel) (Lee et al. 2014) and a novel curcumin derivative (1,7-bis(3-methoxy-4-(prop-2-yn-1-yloxy)phenyl) hepta-1,6-diene-3,5-dione) (40 μM/48h, in the myeloid leukemia cell line, K562) (Lopes-Rodrigues et al. 2017). One of the important

anticancerogenic effects of sesquiterpenes besides their inhibitory effects on P-gp/ABC/MDR-1 pathway is Y box binding-1, YB-1. The sesquiterpene lactone (6-0-angeloylplenolin, 1.4 μM/24h, in the colon carcinoma cell line, HCT-8/VCR) decreases the sensitivity to vincristine and adriamycin (Li et al. 2018) by inhibiting YB-1, which is a member of a family of DNA-binding proteins that contain a cold shock domain. On the other hand, any elevation in environmental temperature increases the cancer cell's susceptibility to chemo-and radiation therapy, like the attenuation in cell survival in the absence of any heat application by down-regulation of the cold shock protein. What the sesquiterpene does here is the inhibition of YB-1 nuclear translocation in cancer cell while suppressing cold shock protein domain in YB-1. This inhibition and the elimination of the function for the adaptation of cancer cell to environmental heat change of the cold shock protein domains (e.g. RNA binding motif protein 3, RBM3) and cold inducible RNA binding protein (CIRBP) in YB-1 creates a significant stress (Zeng et al. 2009). This stress leads to increase in sensitivity to chemotherapy like in the administrations of vincristine and adriamycin (Li et al. 2018). Unfortunately, there is no study to highlight the effect of any food bioactive compound, except curcumin, on cold shock proteins. Such effects of food origin compounds need to be studied urgently to be able to form an anti-cancer diet to follow during the administrations of MDR1/P-gp/ABC protein inhibitors. With the current data, a sesquiterpene rich diet which is supplemented by the plants from the following families might be useful. The sesquiterpene families, according to the latest findings, which inhibit the P-gp/ABC/MDR-1 pathway are as follows; *Cactaceae*, *Solanaceae*, *Araceae* and *Euphorbiaceae* (Canales et al. 2005), *Casearia sylvestris* (Pereira et al. 2017), *Alpinia oxyphylla Miq.* (Shi et al. 2014), *Mikania variifolia*, *Mikania micrantha* and their dichloromethane extracts (2.1 μg/mL) (Laurella et al. 2017), *Polyalthia longifolia* Thw. (Annonaceae) (Ogunbinu et al. 2007), *Alternaria alternate* and *Fusarium oxysporum* (Weikl et al. 2016), *Cichorium glandulosum Boiss et Huet* (Yang et al. 2012), *Cinnamosma fragrans* (Quero et al. 2016), a novel derivative of sesquiterpene dilactone, DETD-35 (synthesized from deoxyelephantopin, 2.5 μM/72h, in the breast cancer cell line, MDA-MB-23)

(Nakagawa-Goto et al. 2016), the sesquiterpene lactones; artemisinin, artesunate and dihydroartemisinin (5 μM/24h each, in the leukemia cell line, K562), costunolide (9.8 μg/mL/48, in the synovial sarcoma cell lines; SW-872, SW-982 and embryonal rhabdomyosarcoma cell line, TE-671) (Kretschmer et al. 2012), the essential oil of *Myrica rubra*, valencene (25 μM/72h, in the ovarian cancer cell line, SKOV3) (Ambroz et al. 2017), dihydro-B-agarofuran sesquiterpene (from *Celastraceae* plants; *Maytenus cuzcoina*, *Maytenus canariensis*, *Maytenus magellanica* and *Maytenus chubutensis* (100 μM/72h, in the multi-drug resist cellosaurus cell lines, NIH-3T3, MDR1-G185, MDA-MB-231 and MDCKII) (Munoz-martinez et al. 2004). The anticancerogenic effect of the sesquiterpenes should not only be attributed to the inhibition of MDR/P-gp/ABC protein pathway. For example, a sesquiterpene lactone from *Siegesbackia glabrescens* (20 μM/30h) has been claimed to inhibit Hedgehog signaling in pancreatic cancer cell line, C3H10T1/2 (Lee et al. 2016). Similarly, the two sesquiterpene lactones from *Artemisia lavandulaefolia* (artelavanolide A, 146.92 μM IC_{50} value and artelavanolide B, 137.40μM IC_{50} value) in a very new study inhibited the cancerogenic and inflammatory cytokine, COX-2 (Lü et al. 2018). The only study currently about the effect of sesquiterpenes on oxidative stress and ROS production in a parasite, *Leishmania Mexicana,* informs that the antiproliferative effect of mexicanin I, dehydroleucodine, psilostachyin and psilostachyin C, are antagonist of glutathione. The active sesquiterpene lactones increase the generation of ROS between 2.7 and 5.4 (Barrera et al. 2013). Although the study uses a parasite as study material instead of a cancer cell line, it clearly indicates to the potential use of the lactones as synergistic with ROS inducing anticancerogenic agents. Another novel sesquiterpene lactone isolated from *Eupatorium Lindleyanum DC*, *eupalinomide O* (8 μM/24h) inhibits the breast cancer cell line, MDA-MB-468, by suppressing the antiapoptotic protein Akt (Yang et al. 2016). Eudesmane (C15H28)-type sesquiterpene lactone, (115)-2α-bromo-oxoeudesmano-12, 6α-lactone (50 μM/4h) inhibits NF-kB and lymphotoxin B- induced breast cancer (Quach et al. 2017). The sesquiterpene lactone, 7-hydroxyfrullanolide from the methanolic extraction of fresh flowering and fruiting heads of *Sphaeranthus indicus* inhibits the cancerogenic cytokine (IL-6/STAT3)

pathway on human peripheral blood mononuclear cells (Fonseca et al. 2010). One other anticancerogenic effect of the sesquiterpene lactones is due to their inhibitory effects on VEGF while suppressing angiogenesis. Confirmingly, deoxyelephantopin (DET) (2.5 μM/72h, in the breast cancer cell line, MDA-MB-23) was claimed to inhibit VEGF and angiogenesis (Nakagawa-Goto et al. 2016). Under the highlight of the findings above, beside sesquiterpenes, curcumin and curcumin rich foods; turmeric and ginger, EGCG and EGCG rich foods like 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, silymarin; *Silybum marianum L.* (milk thistle) (Karimi et al. 2011), lignin rich sources; barley, buckwheat, emmer, maize, millet, oat (Durazzo et al. 2013), wogonin and neobaicalein sources; *Satellaria litwinowii* root, *Scutellaria baicalensis* root (Tayarani-Najarani et al. 2012; Khan et al. 2017), procyanidine rich foods; blueberries, cultivated highbush, lowbush, cranberries, blackberries, Marion berries, raspberries, strawberries, blackcurrant, cherries, green grape, apple, pear, nectarine, plum, kiwi, date, banana, squash, sorghum, bean, red kidney, barley, black eye peas, black bean, hazelnut, pecan, pistachio, almond, walnut, peanut, cashew, chocolate, cinnamon and cury (Gu et al. 2004), baicalein source; *Scutellaria baicalensis Georgi* (Huang et al. 2017), myricetin rich foods; grape, orange, berries, sweet potatoes, parsley, bean, herbs, tea (Devi et al. 2015; Harnly et al. 2006), biochanin A rich sources; red clover, soya and its products, kudzu and hops (Clarke et al. 2008), resveratrol rich foods; peanuts, grapes, blueberries, quercetin rich foods; onion, kale, broccoli, lettuce, tomatoes, asparagus, red leaf, lettuce and green pepper, genistein rich foods; currants, raisins, satsumas, Brazil nut, chestnut, coconut, bazelnut and sesame seeds, kaempferol rich foods; tea, broccoli, apple, strawberries, beans, kale, endive, leek, tomato, grapes, blueberries, cherry, parsley, plum, apricot, onion, herbs; *Ginkgo biloba*, *Tilia* spp., *Equisetum* spp., *Moringa oleifera*, *Sophora japonica* and chrysin rich food/pnat products, e.g. propolis, are the other components which should have been exist in a cancer diet during the treatments with the inhibitors of MDR/P-gp/ABC protein pathway.

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DELETING MEMORY, ONE OF THE NOVEL APPROACHES IN ANTICANCEROGENIC TREATMENTS, AND ITS ASSOCIATION WITH THE FOOD BIOACTIVE COMPOUNDS

Inflammasomes are consisted of a group of cytosolic multiprotein complexes from the sensor proteins of the NOD (nucleotide-binding oligomerization domain)-like receptor (NLR, intracellular sensors of PAMPs, the pattern recognition receptors in which pathogens are detected by the cells of immune system) family, the adaptor protein ASC (a molecule which mediates innate immune signaling by binding the interaction between the pathogen recognition receptors and caspase 1 in inflammasome complexes). These multiprotein complexes are produced by the NLR proteins; NLRP1, NLRP2, NLRP3, NLRP6, NLRP7, NLRC4 and AIM2. The cleavage of caspase-1 and processing of pro-IL-1B and pro-IL-18, leads to the induction of pyroptosis which is a form of cell death (Sahoo et al. 2011). One of the most unexpected findings about cancer formation points out an unrecognized mechanism which induces the production of the inflammatory and cancerogenic cytokine, IL-22, by cancer cells from the memory of CD4+ T cells via activation of the inflammasome, NLRP3, and the release of IL-1B to promote tumor growth. The findings belong to Voigt et al. (2017) clearly present the dilemma which remains uncovered for decades. The dilemma is also the main reason for the incapacity of the current anticancer treatments and nutrition. The dilemma indicates that cancer cells can produce the pro-inflammatory and pro-cancerogenic cytokine, IL-22,

using the memory of the innate immune cells, CD4+T, while increasing the inflammasomic activity and release of another cancerogenic cytokine, IL-1B, to promote tumor growth. More important is that cancer cells, like the cisplatin-resistant ovarian cancer cells, can kill CD4+T cells after they use their memory (Li et al. 2018). According to the findings, the maintenance of disintegration between CD4+T cells and cancer cells, IL-1B and the cytokines by the following chemotherapeutics and food bioactive comounds which inhibit the pathway of CDT +T cell/IL-18,22/IL1B, might have been a novel and effective approach though it might have side effects on immune system. These chemotherapeutics and food bioactive compounds which inhibit the pathway of CD4 +T cell/IL-18,22/IL1B are; leflunomide, CTLA4-Ig, the CD4+ T cell antibodies; cylosporin, tacrolimus, methotrexate (Lorenz 2003), chloroquine (Schmidt et al. 2017), gemcitabine (Glenn et al. 2018), 4,4 prime-diisothiocyano-2,2prime-dihydrostilbenedisulfonic acid disodium salt (Delpire and Lauf 1992), palmitic acid (Lee 2009), I-BET-762 (a small molecule that occupies the acetyl-lysine binding pocket of BET proteins, bromodomain and extraterminal domain proteins that regulate gene expression) (Bandukwala et al. 2012), a new inhibitor of Janus kinase 3 (a tyrosine kinase which are responsible for signaling of cytokine receptors), CP690,550 (Migita et al. 2011), I3C (50 μM or 2000 ppm I3C daily supplementation of mice for 58 weeks) (Liu et al. 2017), quercetin (0.05 % quercetin containing diet for 18 weeks or 50 μM/16h in dentritic cells) (Kobori et al. 2016; Huang et al. 2010), curcumin (200 μg/mL, in CD4+ T cells) (Kim et al. 2013), amygdalin (10 mg/Kg/d for 4 weeks by intraperitoneal injection in mice) (Lv et al. 2017), limonene (8 mM, in CD4+ T cells) (Lappas and Lappas 2012), apigenin (75 μM/5d, in CD4+ T cells) (Xu et al. 2008), fisetin, morin and hesperetin (35μM/72h, in human peripheral blood monocytes) (Verbeek et al. 2004). The findings of Verbeek et al. (2004) are significant since they clearly remark the difference in anticancerogenic potential due to the difference in chemical structure of the food/plant bioactive compound. For example, all of the flavonoids are aglycones (the compounds which remain their glycosyl group, the fragment which contains a vacant point of attachment that would form if the hydroxyl group on the hemiacetal or hemiketal carbon in a cyclic monocaccharide

molecule were removed). Flavonoles contain one H bond and one OH whereas flavonones do not have. The flavones contain one H bond but not contain OH (Fabre et al. 2001). The most remarkable point in the study of Verbeek et al. (2004) is that flavones (e.g. apigenin and luteolin), but not flavonole (e.g. morin) or flavonone (e.g. hesperetin), are effective inhibitors on the T cells. According to the findings of the study, apigenin rich foods; like; parsley and celery and luteolin rich foods; broccoli, pepper, thyme and celery (Lopez-Lazaro 2009) should better be included in cancer diet instead of morin rich foods/plants, e.g. almond, guava, old fustic, osage orange, *Acridocarpus orientalis* (a plant belongin to the family *Malpighiaceae*), onion, apple, tea, coffee, cereal grains (Choudhury et al. 2017) and hesperetin rich ones, e.g. orange (Morand et al. 2011), during the treatments which administer CD4+ T cell inhibitors. If the subject is a healthy individual who targets cancer protection by boosting immune system, then the opposite of this approach, a nutrition which includes morin and hesperetin rich foods, might be useful. On the other hand, oleoresin (semi-solid extracts composed of a resin and oil from basil, capsicum, cardamom, celery seed, cinnamon, clove bud, fenugreek, marjoram, nutmeg, parsley, pepper, rosemary, sage, thyme, turmeric, vanilla) and its components; gingerol, shogaol and zingeron (250 μg/mL/96h, in human peripheral blood lymphocytes) (Tejasari 2007), L-arginine (3 mM/96h, in CD4+ T cells) (Geiger et al. 2016), licorice and its constituents; isoliquiritigenin and naringenin (1 mg/mL/4d, in Treg cells) (Guo et al. 2015), kakkonto (500 mg/Kg, a traditional Japanese herbal medicine, originated in China and composed of the medical plants; *Puerariae radix,* 23.5 %, *Cinnamomi cortex,* 18.8 %, *Zizyphi fractus,* 17.6, *Paeoniae radix,*11.8%, *Ephedrae herba,* 17.6, *Zingiberis rhizome,* 5.9 %, and *Glycyrrhizae radix,* 11.8%) diet supplementation of mice (Yamamoto et al. 2016), sitostanol (saturated derivatives of plant sterols with LdL-cholesterol lowering effect, 1.2 μM/7d, in peripheral blood mononuclear cells) (Brüll et al. 2012) and lycopene (2-9 μg/mL, in peripheral blood mononuclear cells) (Mills et al. 2012) increase the rate of T cell proliferation and therefore, might be contraindicated during the anticancer treatments which administer the CD+ T cell inhibitors. In contrast, the same sources in food/plant origin might be useful in cancer

protection by inducing T cell proliferation and boosting immunity for only the healthy individuals. When the interactions of T cells with the cancerogenic pathways and proteins are concerned, it is informed that the activation of Hedgehog signaling inhibits expressions of CD4 and cell surface of CD5 (Rowbotham et al. 2007). Otherwords, the Hedgehog inhibitors induce T-cell proliferation and activation and thus, might be contraindicated with the chemotherapy which aims CD4+ T cell inhibitions and might suppress the potential to eliminate the risk of the copied data transfer from CD4+ T cells by cancer cells. So, it may be vitally important to note that T cell inhibition is antagonistic with inhibition of Hg signaling. Similarly, the foods/plant bioactive compounds and their rich sources which inhibit Hg signaling might also be antagonistic with the foods/plants which inhibit CD+ T cell proliferation and activity. CD4+ T cells themselves generate ROS via nicotinamide adenine dinucleotide phosphate (NADPH) oxidase expression and electron transport chain activity. For this reason, ROS and redox have been shown to play significant role in regulatory T cell-mediated suppression while ROS inhibitors lead to CD4+ T cell hyporesponsiveness (Previte and Piganelli 2018). Accordingly, the chemotherapeutic agents and foods which target cancer cells by inducing ROS production might strongly be contraindicated with the chemotherapeutic agents and foods/plants which inhibit CD4+ T cell expression and proliferation. On the other hand, the anticancerogenic potential of the agents/food/plant origin bioactive compounds which activate ROS production might be enhanced by the agents/food/plant bioactive compounds which activate CD4+ T cell expression and proliferation. When VEGF and CD4+ T cell association is analyzed, VEGF has a direct suppressive effect on the T cells, (Gavalas et al. 2012) which is also confirmed by Shin et al. (2009) and Ohm et al. (2003). With the present findings, VEGF inhibitors should better be avoided in the anti-cancer treatments which target the inhibition of copying from T cell memory and T cell activity. When the association of the Erk (Extracellular signal-regulated protein kinase), CD4+ T cells and food bioactive compounds is considered, the main determiner appears as the isoform of Erk. Although Erk1 is dispensable for CD4+ T cell proliferation and activation, Erk2 has a significantly important role on

the early phase of CD4+ T cell proliferation. CD4+ T cell proliferation is suppressed in the absence of Erk2. Furthermore, the down-regulation of DNA methyltransferase (DNMT) and increase in phosphor-Smad2/3 (both are the similar proteins that are the main signal transducers for receptors of the transforming growth factor beta, TGF-B superfamily which is critically important for cell development and growth) have often been observed in the absence of Erk2-/CD4+ T cells (Chang 2011). The decrease in DNMT and increase in TGF-B signaling is also induced by the anti-apoptotic protein, Foxp-3 (the transcription factor expressed by T regulatory cells, Treg). Here, Foxp-3, the transcription factor is a key point which needs to be highlighted. The factor is expressed in regulatory T (Treg) cells that regulate hemostasis and self-tolerance when they infiltrate into tumor cells (Szylberg et al. 2016). This function might also be exploited by tumor cells because CD4+ T cells have a strong ability to adapt microenvironment because of the factor. But cancer cells might have copied the information from the CD4+ T cells via the factor and gain hemostasis and tolerance. All these interactions between Erk/MAPK, Treg cells and CD4+ T cells put forward a crucial possibility that Erk/MAPK inhibitors and food/plant bioactive compounds and their sources which inhibit Erk/MAPK might have a synergism with the treatments which inhibit CD4+ T cell proliferation (Table). Such combinations might have been able to eliminate the risk of data transfer and copying of cancer cells from CD4+ T cells by using Foxp3 (the gene which is mainly expressed in CD4+ T cells and has a suppressive role in the immune system like the inhibitions of IL-2 and NF-kappaB).

T helper type 17 (Th17) cells and Treg cells both of whose common precursor cell is CD4+ T fulfill opposite functions. Th17 cells cause autoimmunity and inflammation whereas Treg cells inhibit autoimmunity and inflammation, instead, maintain immune homeostasis (Lee 2018). Cancer cells are willing to demonstrate their perfection in adaptation into the microenvironment which alters the numbers and ratio of the T cells. While there is an accumulation of both Th17 and Tregs as combined with the tumor lymphocytic infiltration of the patients in the early stages of gastric cancer, the ratio of Th17 decreases and Treg

cells increase with the progression of cancer. However, there is no any definite relation among the ratios and expression levels of Th17, Tregs, IL-21 and 23 (Maruyama et al. 2010). The findings of Maruyama et al. (2010) reveals a probability that Th17 cells have an antagonism with Tregs and cancer cells might exploit this antagonism. If Th17 cells decrease as Treg cells increase then it is obvious that Treg cells have been exploited by cancer cells for their homeostasis (adaptation) and defence against Th17 and CDT cells. The increase in Treg cells also induces Foxp3 (Zhou et al. 2009). On the other hand, a diet containing 1% DHA and 1% EPA when compared with the diet containing 2 % AA decrease the amounts of Th17 and IFN-Ɣ (Shoda et al. 2015). Similarly, the diet supplementation which contains 10% safflower oil in rats reduces Th17 cells (Allen et al. 2014). Unfortunately, both studies as the only ones about Th17, IFN-Ɣ and Omega PUFAs associations, do not give the net EPA/DHA and/or AA intakes as 'gram' in diets, instead, the omega fat intakes are informed with ambiguous expressions, like 'the diet containing 1% DHA or 10% safflower oil, rather than definite counts. What sems clear about the status of Omega PUFA preference in cancer treatments is that the fatty acids which are known as anti-aging and protective against many diseases and disorders might not have the same benefits with the progress of cancer since they might gain cancer cells the ability of homeostasis and defence to T helper and CDT cells by increasing the ratio of Treg cells and Foxp3 induction due to the increase in Tregs cells. In spite of many benefits of the fatty acids in a healthy metabolism, it may be a smart and useful approach to avoid from these fatty acids particularly in the later phases of cancer and during the treatments which administer the CD4+ T cell inhibitors, e.g. cyclosporine, tacrolimus and methotrexate, and the food/plant bioactive compounds which inhibit CD4+ T cells, e.g. apigenin and luteolin, because of the risk of increase in amounts of Treg cells. On the other hand, the GRP94-deficient CD4+ T cells cannot undergo activation-induced glycloysis due to defective Ca_2+ mobilization through the pharmacological blockade of the ERCa_2+ channel inositol triphosphate receptor (IP3R). Therefore, they decrease in number (Thaxton et al. 2017). The findings clearly indicate that GRP94 and GRP78 inhibitors suppress CD4+ T cells and therefore the chemotherapeutic agents

and food/plant bioactive compounds and their sources which target tumor cells by inhibiting CD4+ T cell expression and activity might benefit from GRP94 inhibitors; radamide, bnlm and kung29 (Crowley et al. 2017). Similar to GRP94, another chaperon, GRP78, induces the expression and activity level of CD4+ T cells (Bon et al. 2014). The pro-inflammatory and cancerogenic COX-2-PGE2-EP pathway suppresses the dentritic cells (DCs) and natural killer (NK) T cells (Liu et al. 2015). Therefore, COX-2 inhibitors might inhibit CD4+ T cell suppression and might enhance the anticancerogenic potential of the agents/foods/plants/ their bioactive compounds which inhibit tumor progress by decreasing the proliferation rate of cancer cells. Accordingly, GRP78 inhibiting food/plant bioactive compounds might help for the suppression of CD4+ T cells. But, if the approach is the suppression of CD4+T cells, COX-2 inhibiting chemotherapeutic agents and food/plant bioactive compounds might be contraindicated since COX-2 inhibition block CD4+T cell suppression.

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ONE OF THE HOTTEST DEBATES IN ANTI-CANCER NUTRITION, AMYGDALIN, IS IT ONLY AN EXAGGERATION OR PROMISING?

Leatrile is the simpler semisynthetic version of amygdalin, a cyanogenic glycoside (a agylcone with a cyanide group) which is derived from the aromatic amino acid phenylalanine. The glycoside is 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*) and bamboo (*Bambusa arundinacea Wild*) (Femenia et al. 1995; Haque and Bradbury 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 a cyanogenic diglucoside with a formula $C_20H_{27}NO_{11}$, a molecular weight of 457:42 g and a chemical name of D(1) Mandelonetrile-betaglucoside-6beta-D-glucoside (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 (Figure 5). The glycoside is ultimately decomposed into benzaldehyde and hydrocyanic acid (HCN), while the later one is the main poisonous substance (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) (Figure 5). The cyanogenic diglucoside inhibits the expressions of c-Fos (proto-oncogene), TNF-alpha and IL-1beta (an important mediator of the inflammatory response) (Hwang et al. 2008). It decreases the amounts of microtubules and microvessels in rats followed by its intraperitoneal injection (3 mg/Kg) (Mirmiranpour et al. 2012). Amygdalin (1.25-10 mg/mL), like the high-dose arginine/NO (($\geq$400 μM), diminishes phosphorylation of Akt, cdk and cyclin components (the cell cycle regulating proteins), arresting G1 while leading to DNA repair (Makarevic et al. 2014). It also increases the expression of p53, p21 and the activity of caspases that results in G1 arrest, while it inhibits the phosphorylation of RICTOR, the protein which regulates cell growth and proliferation (Shiota et al. 2006) (Figure 5). The diglucoside (10 mg/mL/24h or 2 weeks, in the renal cell carcinoma cell lines, RCC and Caki-1 and kidney carcinoma cell lines, KTC-26 and A-498) induces a marked decrease in the expression of the cell cycle, activating proteins, cdk1, cdk2, cdk4, cyclin A, cyclin B, cyclin D and D3 (Juengel et al. 2016), which significantly leads to apoptosis. The cyanogenic glycoside analogues, dhurrin and prunasin (10^{-4}-10^{-10} M %), are able to reduce the expression levels of the inflammatory cytokines; IL-6, IL-8, IL-23 (the cytokines that are in close relation with tumor progress) and Hsp70 (the antiapoptotic chaperon and the signal activator of IL-6, STAT3) (Paoletti et al. 2013). Finally, amygdalin activates the pro-apoptotic molecule, p38 mitogen activated protein kinases (p38 MAPK) (Lee and Moon 2016). The inhibition of TNF by suppressing the VEGF induction, as one of the most common anticancer approaches, might 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). Treatment of the human prostate cancer cell line, DU145, and the human prostate adenocarcinoma cell line, LNCaP, with amygdalin (extracted from *armeniacae* semen by hatching from the shell and concentrating and recrystallizing it with ethanol) induces apoptosis. The apoptotic effect of the glycoside on these cell lines exhibits its anticancer effect by increasing the expression of the pro-apoptotic protein, Bax, and caspase 3 enzyme activity while it inhibits the expression of the anti-apoptotic protein, Bcl-2 (Chang et

al. 2006). The anticancer effect of the glycoside (2.5-80 mg/mL) due to the increase in the ratio of Bax/Bcl-2 was also confirmed in the breast cancer cell lines, MDA-MB-231 and Hs578T, the human cervical cancer cell line, HeLa, and the human colon cancer cell line, COLO201, by Lee and Moon (2016), Chen et al. (2013) and Kim et al. (2005).

Obviously, the most crucial and controversial point is the amount of the cyanogenic glycoside which may be toxic and not tolerable above a certain limit. Acute cyanide toxicity (ACT), the severe side effect of the glycoside, can occur between 0.5-3.5 mg/Kg and totally 250 mg in human (Gosselin et al. 1976; Rasalkar et al. 2010) (Figure 5). On the other hand, the dose of amygdalin which forms an anti-cancerogenic effect by inhibiting TNF-alpha, c-Fos and IL-beta expressions is ≤0.005 mg/Kg (Hwang et al. (2008). So, the dose seems very safe when compared with the dose, 3.5 mg/Kg, that causes ACT. Excess consumption of apricot kernels (to produce more than 1 mg/L cyanide in blood) may cause the poisoning while the fatal dose of hydrogen cyanide is 0.5 mg/g (Figure 5). Amygdalin content of apricot is 6.0-15.8 mg/g, but the amount may be as high as 55.6 mg/g as dependent on variety. The seeds of courgette, melon, cucumber and marrow are 0.21, 0.12, 0.07 and 0.06 mg/g, respectively. The amount in squash is 0.11 mg/g, while it is between 0.03 and 0.06 mg/g in processed peach juice, prune juice and slices. Processed toasted almond, almond milk, almond cocoa dessert, almond flour and Marzipan have 0.12, 0.05, 0.04, 0.03 and 0.02 mg/g amygdalin concentrations, respectively. While amygdalin contents of sweet and bitter almonds are reported to range from 0 to 68.5 mg/g, depending on the cultivar, green plum has the highest as 17.5 mg/g, followed by apricot (14.4 mg/g), black plum (10 mg/g), peach (6.8 mg/g), red cherry (3.9 mg/g), black cherry (2.7 mg/g) and purple, yellow and red plums (0.44-2.16 mg/g). On the other hand, nectarine has the lowest amygdalin content (0.1 mg/g) among the stone fruit seeds (Bolarinwa et al. 2014). It may also be important to remind the declaration of the Panel of the European Food Safety Agency. The Panel reported that acute cyanide toxicity had occurred in adults who had consumed 20 kernels of apricot while ≥5 amounts appeared to be toxic in children (EFSA 2016).

Under the highlight of the data mentioned above, it is clear that the glycoside has a significant anticancerogenic effect while its safety is closely dependent on its amount. Therefore, the 'amount' and 'concentration' should definitely be taken into consideration before any bias or blame. More important is that this substance is not the one that can be immediately rejected or prejudiced by ignoring its strong anti-cancerogenic effect. The crucial status of amygdalin in anti-cancer treatments and nutrition should not only be restricted with its inhibitory effects on the important cancerogenic proteins and pathways mentioned above. It has also an effect on trophoblasts, the cells which form the outer layer of a blastocyst (a tissue structure 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 pregnant and embryo, making them vulnerable to cancer (Griffin 1997). The trophoblasts, though they are the formers of the embryo, do exhibit the characteristics of cancer and spread over the uterus wall. If they are not destroyed by the chymotrypsin enzyme of pancreas just after the embryo formation, they can be transformed into stem cells which carry cancerogenic genes. The theory is also supported by a very old theory of Krebs and Beard (1950) which claims 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). The same important key point 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 tumour as a response to previously mentioned intramural parasitization by trophoblasts (Ross 2015). 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, the expression of the same cells might also be upregulated as a part of a healing process, in a response to a wide range of carcinogens from allergens, nutrient compounds and toxic minerals to microorganisms. The cancerogenic potential of trophoblasts and the probability to prevent them from forming tumour, have been informed by the current studies. The

treatment of the trophoblast cell line, JEG-3, with gastrokine 1, GKN1, a member of gastrokines, the stomach-specific suppressor genes which are expressed in gastric cells, reduces the migration of the trophoblast (Fahlbush et al. 2015). Futhermore, the transfection of GKN1 into the gastric carcinoma cell line, AGS, and gastric epithelial cell line, HFE-145, causes inactivation and reduced expression of NF-kB and COX-2 (Yoon et al. 2013), while inhibiting gastric tumor progression in mice (Menheniott et al. 2016). But, neither the gastrokine administration to reduce tumor progression by inhibiting trophoblast nor the effect of amygdalin or any other food bioactive compound on gastrokine expression have been studied yet. Human Chorionic Gonadotropin (hCG), the hormone which is produced by the embryo following implantation (the very early stage of pregnancy at which the embryo adheres to the wall of the uterus) (Cole 2009), has currently been used for the detection and monitoring of pregnancy. But, it is also a very sensitive and specific marker for trophoblastic tumors of the placenta, germ, and testicular germ cell. Elevated hCG 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 the serum of 67 % of patients with malignant ovarian tumors (Lenhard et al. 2012). If the theory of Krebs and Beard (1950) and Griffin (1997) which claims that the stem cells or at least many cancers are trophoblasts in origin is correct and even a very few of them may serve as a precursor for tumor formation, can amygdalin destroy these trophoblasts and subsequently decrease the levels of hCG with or without gastrokine?.Still, there is no any other study to highlight the question about the association of amygdalin and other food bioactive compounds with trophoblast, gastrokine and hCG except the very old review of Greenberg (1980). The review disclaims the anticancer potential of amygdalin while it considers many other causative agents for cancer like viruses, heredity, physical and chemical agents more than the anti-cancerogenic potential of the glycoside. The author regards trophoblasts as one of the minor causative factors in a minor range of cancer types, limiting their effects into the cancers of female and male reproductive system, like chorioepithelioma. 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, since there is no study which analysis the link between the 'cancerogenic agent and trophoblast'. In spite of these unanswered questions about the association of amygdalin with trophoblast, gastrokine and hCG, there is still no study to highlight these questions. However, the most likely reason might be the side effect of the glycoside, 'cyanide toxicity'. Confirmingly, one of the very few studies administered 3 g amygdalin as intravenous which is higher than the toxic limit '250 mg/d', and did not find any improvement in symptoms, but cyanide toxicity (Moertei et al. 1982). On the contrary, 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. The enzyme activity was determined as the highest in Caco-2, followed by HT29 and T84, all of which are colorectal adenocarcinoma cell lines (Arafa 2009). Although the study of Kim and Jin (2001) is the only study about the association of beta-glucuronidase and cancer, it determined beta-glucuronidase activity 1.7 times higher in colon cancer cells than healthy cells which may indicate to a likely higher activity of beta-glucosidase in cancer cells. The momentous point here is the possibility of higher vulnerability of cancer cells to amygdalin if they have higher beta-glucosidase activity than healthy cells. Such a higher beta-glucosidase activity in cancer cells might release more cyanide and benzaldehyde from glucose which might result in a less amygdalin toxicity on healthy cells. Therefore, new studies to show the activity levels of beta-glucosidase in different types of cancer cells are urgently needed. Only after the determinations, the hesitations about the amygdalin's side effect might have been abated. In the latest corner of anticancerogenic food bioactive compounds, the study of Syrigos et al. (1998) might be a cornerstone, since the authors conjugated the enzyme to a tumour-associated monoclonal antibody with amygdalin to activate and direct amygdalin as specific to the tumor site, without any systemic toxicity which is often associated with chemotherapy. This approach, the '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 cell as combined with amygdalin and beta-glucosidase might gain amygdalin a novel anti-cancer agent potential without any systemic toxicity. When it comes to the final and the most important stage, amygalin administrations could gain a much wider application field by limiting its side effect, 'the cyanide toxicity', by using rhodanese, an enzyme which is exist in human (Whitehouse et al. 1988). The enzyme binds cyanide of amygdalin to thiosulfate 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% toxicity of cyanide and it is readily eliminated by the kidneys. Moreover, thiocyanate which is taken orally is completely absorbed by the body, with a distribution volume; 0.25 L/Kg and a 3 day half-life (Cailleux et al. 1988). Furthermore, thiocyanate toxicity does not possess any serious problem, even in its intravenous infusion as sodium nitroprusside, one of the main anaesthetics which is converted into thiocyanate by rhodanase (Schulz 1984). The cyanide in amygdalin which is transferred into cells by glucose is neutralized by rhodanese. But, like beta glucosidase activity, the activity of rhodanase differs as being specific to the type of cancer while it may be very different in normal cells. For example, that the activity of the enzyme is significantly lower in lung cancer cells than healthy cells has been claimed by Jamshidzadeh et al. (2001) and their study is the only study which compares the enzyme activity in normal and cancer cells. So, the administration of ADEPT containing amygdalin as attached to monoclonal antibody that is specific to the targeted cancer antigen, might transfer cyanide directly into cancer cells and can kill them. This therapy may also give damage to normal cells because of the cyanide residues which are left behind. On the other hand, a following intravenous rhodanase administration might eliminate or lower this risk. Rhodanese might be injected after the 'ADEPT and amygdalin' to be able to lower this risk, but the time intervals which are required to kill cancer cells by cyanide of amygdalin is the other question. In spite of the questions, there are many studies which claim the anticancer potential of amygdalin. Amygdalin (1.25-10 mg/mL) was shown to inhibit the human bladder cancer cell lines, UMUC-3, RT112 and the urinary bladder cancer cell line, TCCSUP (Makarevic et al. 2014), the

renal cancer cell line, RCC (Juengel et al. 2015) and the human colon cancer cell line, SNU-C4 (Park et al. 2005). Laster and Schabel (1975), and Wodinsky and Swiniarski (1975) observed increase in life span of amygdalin treated animal groups. Stock et al. (1978) claimed 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), Syrigos et al. (1998), and Navarro (1959) were the other scientists who observed significant anti-tumor activities or increases in life-span of patients. On the other hand, Ovejera et al. (1978) did not observe any inhibitory effect on breast and colon cancer tumor cells. Finally, Hill et al. (1976) and Chitnis et al. (1985) did observe significant increase in apoptosis while Koeffler et al. (1980) did not find any selective inhibition of myelogenous leukemia, liver cancer and lymphocytic leukemia cells. One of the most crucial missing points about the currently most debated bioactive compound is the lack of cohort studies to compare its long term/high dose and long term/low dose administrations.

After the answers for the questions above, the studies which use the technology of ADEPT and amygdalin and rhodanase as combined with monoclonal antibody', might even be a pioneer for the future anticancer vaccines.

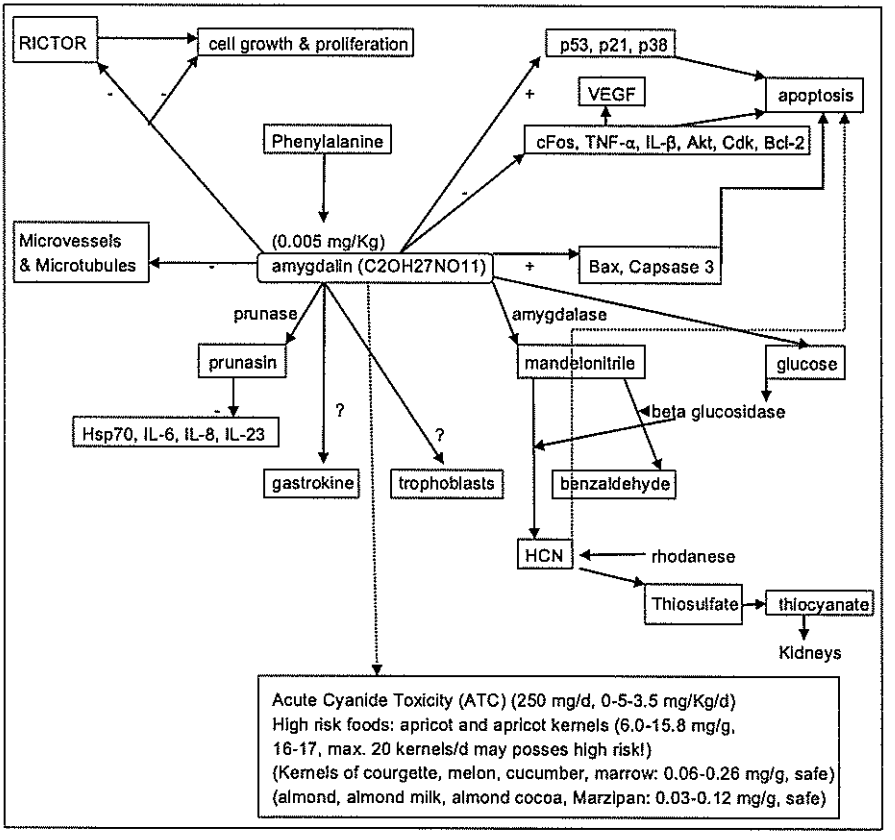


Figure 5. Amygdalin and its association with the pathways in cancer

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THE DILEMMA OF GLUCOSE, FRUCTOSE AND CANCER

Increased flux of glucose and glucose metabolism induce cancer via the proliferation, anti-apoptotic signaling, cell cycle progression and angiogenesis, while cancer cells become more addicted to aerobic glycolysis to produce ATP for their proliferation (Koppenol et al. 2011). The tendency of malignant cells to glucose and apoptosis of cancer cells in a media without glucose were first confirmed by Shim et al. (1998). Currently, it is well known that the diabetogenic glucose concentrations, 11 mM, as compared with 5.5 mM, leads altered expression of genes which promotes cell proliferation in breast, colon, prostate and baldder cancer (Masur et al. 2011). Confirmingly, the reduction in plasma glucose levels and calorie restriction, significantly prolong the survival in tumor-bearing animals (Santisteban et al. 1985; 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). The close link between the higher risk of cancer and glucose uptake might be attributed to an adaptation to intermittent hypoxia in pre-malignant lesions with a microenvironmental acidosis which leads to the formation of acid-resistant cancerogen cells (Gatenby and Gillies 2005). In addition to the close link between glucose and cancer, the higher risk has also been informed for fructose and still remains to be the center of hot debates in public health and nutrition. Both sugars have the same chemical formula, $C_6H_{12}O_6$. The only

difference in their chemical structure is the hemiacetal group from position 1 of the glucose carbon chain and the hemiketal group at position 2 in fructose. This difference has profound effects in the cellular functions and disease processes of fructose (Samuel 2011; Theytaz et al. 2014). For example, normal cells including normal monocytes use glucose as the main metabolic fuel enhancer whereas cancer cells prefer fructose. Notably, the transporter of fructose, GLUT5, its encoding gene, SLC2A5 and their inducing effect on fructose utilization, have often poor prognosis. This effect also indicates a close link between chemical structure and the genetic pathway of the sugar (Chen et al. 2016). The initial difference to contribute to the cancerogenic potential of fructose starts in gut. Followed by decomposition of disaccharides into glucose and fructose, glucose is absorbed through the mucosa layer of gut by a Na-dependent glucose transporter, but fructose is absorbed in duodenum and jejunum by 5(GLUT5), the fructose-specific transporter glucose transporter. Then, both monosaccharides enter the portal circulation of the liver or circulate other organs through specific GLUTs. The transporter which carries glucose into hepatocytes and other cells is GLUT4. Glucose in hepatocytes undergoes glycolysis and is stored as glycogen in liver or can be converted into lipids, amino acids, pyruvate and energy via the tricarboxylic acid (TCA) cycle. The increase in serum glucose is taken under control by insulin which is released from beta cells of pancreas. Insulin release activates glucose transporters on the surface of cells and causes glucose uptake. The increase in glucose uptake promotes glycogen formation in liver while inhibiting glucose-6-phosphate and ATP production. Briefly, either absorption or control of glucose is insulin –dependent. By contrast, fructose is transported into cell by GLUT5 as insulin-independent. This transfer is limited and 70 % of fructose is utilized in liver, but only 30 % is used for the metabolism of other tissues. Another important contributer to the cancerogenic potential of fructose is that, insulin does not have any effect on GLUT5, while it has a significant control on other GLUTs and glucose. Fructose is phosphorylated by fructokinase and converted to glycerol-3-phosphate or glyceraldehydes-3-phosphate. The former is utilized in low-density lipoprotein production and the later is used for ATP synthesis. Also the activation of ketohexokinase by

fructose is essential for ATP production but this activation rapidly depletes intracellular ATP because it metabolizes fructose to produce ATP. The ATP depletion leads to increase in Adenosinine monophosphate (AMP) which is converted to uric acid, a contributer to hypertension, inflammation and cancer (Wang et al. 2015; Yan et al. 2015 and Charrez et al. 2015). Briefly, the insulin-independent fructose metabolism cannot be taken under control and can cause cancer in inflammation origin. Unfortunately, all the mentioned findings made fructose and its rich products like fruits and vegetables as the biggest culprit in cancer, no matter how sophisticated and dual machineries determine the prognose and the very rich anti-cancerogenic nutritional potential of many fructose rich foods have. Some of the media-supported! authorities and even governments! in many countries, have followed a nutrition strategy to restrict daily fructose-uptake in public nutrition. Such trend is still very common in spite of many conflicted and unanswered questions about fructose. First, when fructose activates ketohexokinase and elevates its level during high-fructose diets, the enzyme rapidly metabolizes fructose and depletes ATP levels. Not only healthy cells but also cancerous ones require ATP to survive and proliferate. Could it still be a literally scientific claim that fructose has a significant cancer inducing potential though ATP in cancer cells is depleted by a high fructose metabolism?. Second, glucose is readily converted to fructose via the polyol pathway whereas glucose is metabolized to sorbitol and fructose. Therefore, the limitation of some of the fructose rich food products, from corn-syrup to fruits and vegetables, would be meanless while the precursor of fructose is glucose which is exist in almost all foods in nature in foods from animal origin to plant origin. Moreover, 'fruits and vegetables' which are currently being blamed for cancer risk because of their higher fructose contents seems utterly incomprehensible since this group is also rich in many important anti-cancerogenic food bioactive compounds, namely; quercetin, I3C, leukopen, ascorbic acid, apigenin, sulforaphane and resveratrol, most of which are in a complete synergy with chemotherapeutic agents (which is the main conclusion of the review as well). The dramatic increase in the rate of glucose uptake and lactate production, the Warburg effect', may present an advantage for cell growth. Elevated glucose metabolism decreases the pH due to

lactate secretion and the acidosis has benefits for cancer cells. H+ ions which are secreted from acidic microenvironment of cancer cells into the surrounding environment alter the tumor tissue and enhances its invasiveness. The ability of H+ -ions to change the ionization state of proteins forms the bases of pH sensitivity of cellular behavior, cancer formation and metastasis. Elevated glucose metabolism and adaptations to the increase in H+/H+-equivalent transporters and activity of extracellular carbonic anhydrase (CA), the enzymes that catalyze the rapid interconversion of carbon dioxide and water to bicarbonate and protons or vice versa, give cancer cells the means to manipulate micro-environmental acidity (Swietach et al. 2014). Moreover, poor prognosis for tumours with low pH indicates that acidity leads to a population of cells with the appropriate pH sensing and regulatory mechanisms to thrive and become resistant to some chemotherapeutic agents. The Warburg effect and hypoxia lead to expression of a number of molecular machineries, NHE1 (the Na+/H+ antiporter, a ubiquitous membrane-bound enzyme involved in pH regulation), H+pump V-ATPase (proton ATPase that catalyzes decomposition of ATP into ADP, phosphate and H+), CAs (-9, -12), MCT-1 (Monocarboxylate transporter 1, a protein which is important in ATP production and glucose metabolism) and GLUT-1 (Glucose transporter 1). The over-expression and activation of the proton exchangers and transporters triggers the formation of tumour microenvironment (Asgharzadeh et al. 2017). If glucose is the precursor of fructose and both of them activate the proton exchangers and transporters to form tumor microenvironment under Warburg effect, would it be precisely correct to ignore or exclude glucose, but blame only fructose for cancer risk, a blame which has often been done by media and some authorities?. Furthermore, what is the point of mentioning that fructose is the biggest culprit in cancer risk and should be restricted, while fructose and its precursor glucose are exist in almost all foods including the foods such as fruits and vegetables which are also rich in many anti-cancerogenic food bioactive compounds?. Table 1-5 clearly show the anticancerogenic effects of many of the food/plant bioactive compounds via their inhibitory effects on the most common cancerogenic patways, enzymes and signaling, under the highlight of the findings which are reviewed in this manuscript. Isn't it obvious that

such advices and acknowledgements which suggest fructose restriction would be useless and impractical since it would mean to have eliminated many important and beneficial legumes, fruits, cereals and vegetables with their significant anti-cancerogenic food bioactive compounds?. Would we continue to blame fructose rich fruits and vegetables while some of their food bioactive compounds have already been informed to inhibit the mentioned tumor microenvironment which forms proton exchangers and transporters?. For example, 'the inhibitions of human GLUT1 by resveratrol (100 μM/2h in the human leukemia cell line, HL-60) (Salas et al. 2013), beta carotene (20 μM/48h in BE(2)C cells, in the human neuroblastoma cell line, BE(2)C) (Kim et al. 2014), and EGCG (20 μM/2h in 3T3-L1 adipocytes) (Ku et al. 2014). Additionally, the following isoflavonoids most of whom are exist in fructose rich fruits and herbals e.g., grape, carrot, burdock, apricot, prune and clove (Panzella and Napolitano 2017; Kasai et al. 2000; Chatterjee and Bhattacharjee 2015); vanilic acid, α-coumaric acid, transcinnamic acid, chlorogenic acid, protocatechuic acid, hydroxybenzoic acid, propylparaben (0.11-1.33 μg/mL), guaiacol, 4-methylguaiacol, 4-propylguaiacol, eugenol, isoeugenol, vanillin, syringaldehyde, catechol, 3-methylcatechol, 4-methylcatechol and 3-methocycatechol (2.20-515.98 μM) were informed to inhibit CAs (Karioti et al. 2016) (Figure 6). Finally, another dilemma about the link between fructose and cancer still continues in spite of the rich fiber contents of the foods which are also rich in fructose. Rich content of fiber, either soluble or insoluble, reduces calorie intake and can prevent from high calorie-induced cancer (Shankar and Lanza 1991). Additionally, not all types of cancer, but particularly the risk of incident distal colorectal adenoma and colorectal cancer could be reduced by an elevated dietary fiber intake according to the findings of Kunzmann et al. (2015), Murphy et al. (2012) and 25 prospective studies in the meta-analysis of Aune et al. (2011). Soluble fibers in fruits, vegetables, and grains like oats undergo metabolism in the small and large intestine through bacterial enzymes. These fibers feed probiotics and increase their enzyme activity to convert colon carcinogens (like azoxymethane) into detoxified products. Insoluble fibers which are exist in bran are not metabolized by the enzymes in the probiotic microorganisms in intestine. But, they reduce

the risk of particularly colon cancer by increasing water retention and diluting carcinogens like secondary bile acids which are tumour promoters (Weisburger et al. 1993). When barley, corn, oat, wheat (whole), spinach, tomato, carrot, kiwi, mango, pineapple, grape, orange, plums, strawberry, banana, peach and pear, only very few of the foods with not only high fiber but also rich fructose contents (Dhingra et al. 2012; Barrett and Glbson 2007), are considered, would it be correct to eliminate or limit these fructose rich foods? Putting all the blame on the fructose rich foods, particularly fruits and vegetables while disregarding their rich fiber and bioactive compounds both of which act as anticancerogens, can not be a reasonable and scientific approach. Such approach would have to mean the elimination of all anticancerogenic fibers and bioactive compounds namely, I3C, lycopene, quercetin, lycopene, apigenin resveratrol, sulforaphane, ascorbic acid and toocopherol. Let alone the impossibility of eliminating fructose, glucose and glutamine from diet (which was discussed above in detail), such approach would also have deprived metabolism of the important anticancerogenics such as the mentioned fibers and bioactive compounds.

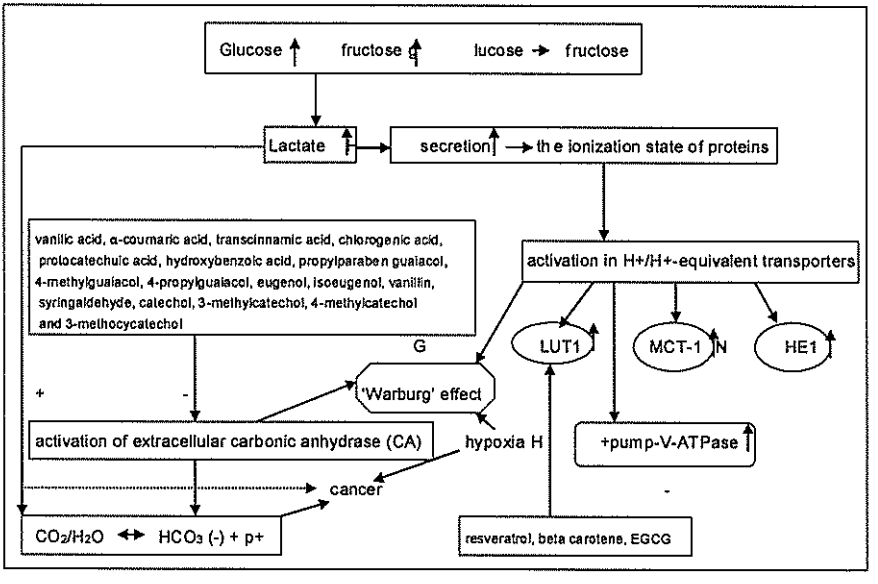


Figure 6. The factors including glucose and fructose which contribute to the progress of cancer.

Resveratrol	EGCG	Kaempferol	Genistein	Quercetin	Lycopene	Apigenin	Amygdalin	Omega 3 PUFAs	Vitamin D3	α-Tocopherol	Ascorbic acid	Curcumin	Baicalein	Daidzein	I3C	β-carotene	
+	+	+	+	+	+	+	+	+	+	-	-						ROS
-	-		-	-		-			-			-	-				Hg
-	-	-	-	-	-	-	-		+	-				-		-	PI3K/Akt/mTOR
-	-	-	-	+		-			?		-	-	-			-	VEGF/HIFα
-	-	-	-	-	-	-		-	-	-	-					-	MMP
-	-	-	-	-		-	-		+	-	-				+		TNF-α
+			+	+		?		+			?	+				+	Nrf2
?				?		-	?		-		-	-			-		MDR
-	+	+		+		+					-						HO-1
	-			-	-	-			-	-							Her2
-	-		-	-	?	-	-	-	-		-	-					mTOR
+	+	+	+	+		+	?			+	+			+	+		Foxo3
-	+	-	+	-	+	-	-		-		-				-		Bcl-2
+	-	+	-	+	-	+	+		+		+				+		PUMA/Bax
-	-	-	-	-	-	-	-		-		-				-	-	Cox2/NFkB
	-	-	-	-		-	-		-	-	-	-	-		-	-	IL-6/STAT3
+	-		-	-	-	-	?		-	?	?				-	-	IL-8
-	-			-	?	?	?		+			-			?		Notch
-	-	-	-	-								-	-				Wnt/B-Catenin
	-	?	?	?	?	-	?		-			-			?		Lin28
-	-	?		?		-						-					PD-1/PD-L1
-	-	-	+	+	-	-		+	-	-	-				+		GRP78/Herp
+	+	+	+	+	+	+			+						+	+	p21
				-	-							-					AP-1
	+	-	-	+	-	+			-		+					-	p38
-	-	-		-	-						-						MMR
-	-	-	-	-		-											MDR/P-gp/ABC
				-		-	-	+				-			-		CD4+ T

Table 1. The effects of the food/plant bioactive compounds on the most common pathways, enzymes and signaling (+: induce -: inhibit ?: unknown

L-arginine	Sulforaphane	Folic acid	δ-Tocopherol	Gingerol	Silymarin	Berberine	Turmeron	Omega 6 PUFAs	Myricetin	Choline	B12	Chlorophyll	α-crypthoxhanthin	Zeaxhanthin	Egg-derived peptides	Lutein	
																	ROS
																	Hg
-	-	?															PI3K/Akt/mTOR
?	-	?	-	-	-	-											VEGF/HIFα
-	-	-					-	-									MMP
+	-	-							-	-	-						TNF-α
	+				+							+	+	+	+	+	Nrf2
+	-	-															MDR
+	+																HO-1
?	-																Her2
+	-																mTOR
-	+																Foxo3
-	-	+															Bcl-2
+	+	-															PUMA/Bax
-	-	-	-														Cox2/NFkB
-	-																IL-6/STAT3
-	-	-	?													-	IL-8
?	+	-															Notch
	-																Wnt/B-Catenin
		+	?														Lin28
-																	PD-1/PD-L1
	+	?															GRP78/Herp
		+															p21
	-																AP-1
-	+	+															p38
+			-														MMR
					-												MDR/P-gp/ABC
																	CD4+ T

Table 2. The effects of the food/plant bioactive compounds on the most common pathways, enzymes and signaling (+: induce -: inhibit ?: unknown

Wagonin	Luteolin	Trigonelline	Retinoic acid	Chrysin	Brusatol	capsaicin	Piperine	Enterolactone	Matairesinol	Laiciresinol	Esculetin	Pinoresinol	Glutamin	NO	campanulin	Astaxanthin	Theophylline	
																		ROS
																		Hg
																		PI3K/Akt/mTOR
																		VEGF/HIFα
																		MMP
																		TNF-α
-	-	-	-	-	-	-	-											Nrf2
						-	-											MDR
	+			+		+		+	+	+	+	+	+	+				HO-1
													?	?		-		Her2
	-						-						?				-	mTOR
	+						+						-	-				Foxo3
																		Bcl-2
																		PUMA/Bax
	-			-														Cox2/NFkB
																		IL-6/STAT3
																		IL-8
																		Notch
																		Wnt/B-Catenin
								?										Lin28
																		PD-1/PD-L1
	-																	GRP78/Herp
																		p21
																		AP-1
																		p38
																		MMR
																		MDR/P-gp/ABC
																		CD4+ T

Table 3. The effects of the food/plant bioactive compounds on the most common pathways, enzymes and signaling (+: induce -: inhibit ?: unknown

Caffeine	Rotundarpene	Y-tocotrienol	Berberine	Hesperetin	Naringenin	Elemental Ca	diosmin	prostratin	myricetin	Δ-tocotrienol	Isorhamnetin	Lupeol	Chlorogenic acid	Procyanidin A2, B2	B6	
																ROS
																Hg
																PI3K/Akt/mTOR
																VEGF/HIFα
																MMP
									-							TNF-α
																Nrf2
																MDR
																HO-1
																Her2
-	-	-	+													mTOR
				-	-											Foxo3
						-										Bcl-2
																PUMA/Bax
							-	-	-							Cox2/NFkB
																IL-6/STAT3
																IL-8
										-						Notch
											-	-				Wnt/B-Catenin
													-	-		Lin28
																PD-1/PD-L1
															-	GRP78/Herp
																p21
																AP-1
																p38
																MMR
									-					-		MDR/P-gp/ABC
				-												CD4+ T

Table 4. The effects of the food/plant bioactive compounds on the most common pathways, enzymes and signaling (+: induce -: inhibit ?: unknown

Biochanin-A	Silibinin	Tangeretin	Vitamin E succinate	Icaritine	Wogonin	Morin	Coumarin	Sesquiterpenes	Limonen	Theopylline	Rotundarpene	
												ROS
												Hg
												PI3K/Akt/mTOR
												VEGF/HIFα
												MMP
												TNF-α
												Nrf2
								-				MDR
												HO-1
												Her2
										-	-	mTOR
												Foxo3
												Bcl-2
												PUMA/Bax
												Cox2/NFkB
												IL-6/STAT3
												IL-8
												Notch
												Wnt/B-Catenin
												Lin28
												PD-1/PD-L1
												GRP78/Herp
+												p21
	-	-										AP-1
			+									p38
												MMR
-				-	-		-	-				MDR/P-gp/ABC
						-			-			CD4+ T

Table 5. The effects of the food/plant bioactive compounds on the most common pathways, enzymes and signaling (+: induce -: inhibit ?: unknown

25.a. Glucose-Fructose and Glutamin interactions in cancer progress

While glucose acts as a precursor of fructose, it is also in a very close relation with the amino acid, glutamine. This relation is a collaboration between the sugar and amino acid to produce energy. Glutamine is converted to glutaminase under the effect of RhoGTPase (a family of signaling G proteins, also known as guanine nucleotide-binding proteins which are involved in transmitting signals from a variety of stimuli outside a cell to its interior) and NF-kB, (the protein complex that controls DNA transcription, cytokine production and cell survival). Glutamate which is formed from glutaminase directly enters to the Krebs cycle of glucose. First criteria which should be vitally considered in determining and evaluating the cancerogenic status of fructose is that glucose is converted first, into glucose 6-phosphate, then, fructose 6-phosphate, fructose 1,6 biphosphate, glyceraldehydes 3 phosphate and after several mid-products, pyruvate is formed. Pyruvate is converted into acetyl CoA, citrate and α-kG (alpha-ketoglutaric acid, a keto acid) to form aspartic acid and mid-products; ATP (the energy) and NAD+ and NADH (the skeletons of amino acids). On the other hand, glutamate from glutaminase of glutamine is converted to α-kG in Krebs cycle to form the energy, ATP and NADH/NAD+, while the same amino acid is finally converted to GSH (glutathione), GABA (gamma-amino butyric acid) and other amino acids (Weigin et al. 2010). In a nutshell, fructose cannot be considered, evaluated or criticized solely. It's status and potential in cancer and other chronic metabolic diseases and disorders can only be evaluated via its close relation with glutamine.

25.b. Fructose has also dual effect with its apoptotic effect, like many other enzymes, signaling, proteins and bioactive compounds in cancer progress

It has apoptotic effectGlucose-6-phosphate dehydrogenase, G_6PDH is the enzyme which catalyzes the binding of D-glucose 6-phosphate to NADP to form 6-phospho-D-glucono-1,5-lactone, NADPH and H+. Therefore, it acts as a NAD binding domain. The NADP(H), as one

of the end products in the reaction, maintains the level of glutathione that protects red blood cells against oxidative damage of free toxic radicals like hydrogen peroxide (Thomas et al. 1991) and is involved in biosynthesis of fatty acids. G_6PD reduces NADP+ to NADPH by oxidizing glucose-6-phosphate and inhibition of G_6PDH impairs many cellular processes that are dependent on NADP(H) (Stanton 2012). On the other hand, the inhibition of Fatty Acid Synthase (FAS), a key enzyme which is involved in lipogenesis and highly expressed in many cancers, stimulates NADP(H) oxidase to generate reactive oxygen species (ROS), leading to induction of apoptosis (Cui et al. 2017). But, fructose has been claimed to inhibit G_6PDH activity which results in the convertion of NAD(P) to NADP(H), the NADP(H) accumulation and apoptosis by NADP(H) (Zhao et al. 1998). NADP(H) also inhibits transfer of the [2Fe-2S](iron-sulfur protein) cluster to an apo-acceptor protein and this inhibition indicates to potential of $NADP_8H$ to inhibit enzimatically active proteins (Zuris et al. 2012) (Figure 7). These findings clearly reveal a significant apoptotic effect of fructose by inhibiting the activity of G_6PDH while converting NAD(P) to NADP(H) and suppressing the enzymatic inhibition of active proteins. On the other hand, ROS production by fructose does not only form via the inhibition of FAS. The chemical structure of the sugar appears as an important contributer to the ROS production of fructose. Unlike glucose, intermediary metabolites from fructose metabolism overwhelm hepatic mitochondrial capacity. Because fructose forms a 5-member fructofuranose ring with steric hindrance from the axial hydroxymethyl groups, more molecules find themselves in the linear form. Thus, their reactive keto group is exposed 7 times more rapidly to fructation of proteins than with glucose (Ahmed and Furth 1992; Lustig 2013), and this might be an important reason for the greater damage on the hepatic mitochondrial capacity of fructose than glucose.

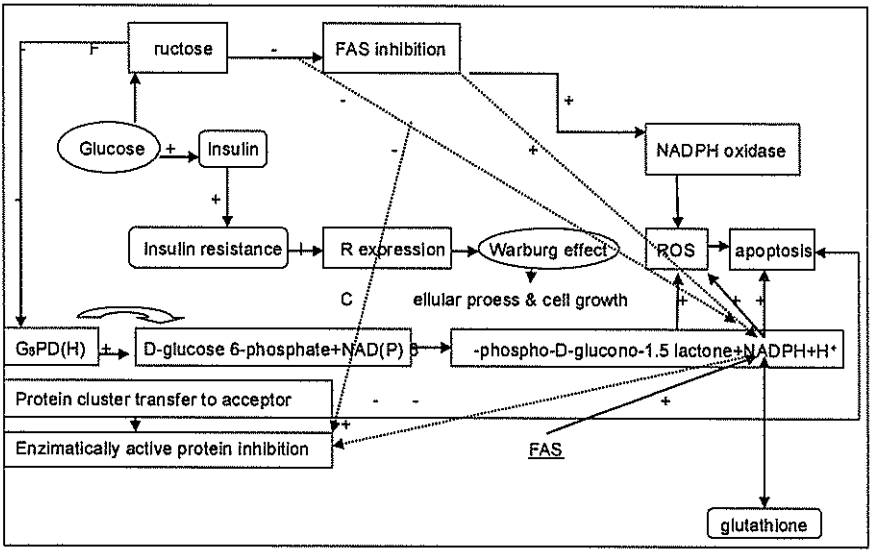


Figure 7. The anticancerogenic effect of fructose by inhibiting active proteins, $G_6PD(H)$ and NADPH.

CtBP, C-terminal binding protein, and the oncogenic transcriptional co-regulators which are overexpressed in many cancer types, increases the activity of GDH, glutamate dehydrogenase, the enzyme which catalyzes amination for cancer cells to assimilate ammonia. Ammonia accelerates the proliferation of cancer cells (Spinelli et al. 2017), while repressing the expression of SIRT4 which inhibits glutaminolysis. So, the axis of CtBP-SIRT4 and GDH induces tumour cell growth, remarkably. One of the most crucial findings in cancer nutrition indicates that low level of glucose supply decrease GDH activity via blocking CtBP and abolishes CtBP binding to SIRT4 and the repression of SIRT4 expression. In contrast, high glucose supply shows higher GDH activity and therefore causes more ammonia production and increases the repression of SIRT4, both of which result in tumour cell growth (Wang et al. 2018). When glutamine existence in muscle tissues and almost all protein rich foods like, beef, chicken, fish, dairy products, eggs, and glucose abundance in almost all foods and finally the close link of glucose with fructose and glutamine are all concerned, the meaningless of blaming only fructose for cancer becomes incontrovertible. Futhermore, limiting glutamine, fructose and glucose rich foods, most of which are rich in nutrients

and medicinal anti-cancerogenic food bioactive compounds, in diet, is not possible in practice. Limiting glutamine, fructose and glucose rich foods inevitably results in malnutrition and limits the intake of essential nutrients and anti-cancerogenic food bioactive compounds which may lead to cancer and other metabolic diseases and disorders. Under all circumstances, criticizing and blaming fructose and fructose rich foods in the foreground do not seem to have any scientific base. Such claims can only be the trendy claims that keep media and some authorities unnecessarily busy while misdirecting public nutrition. Additionally, the previously mentioned insulin-independent metabolism of fructose, the ATP depletion and increase in AMP which raises uric acid as a result of activation of ketohexokinase by fructose enhance the cancerogenic potential of fructose. But, does it make fructose the only most responsible culprit when compared with glucose?.

Park et al. (2008) inform that human subjects have higher level of lipogenesis and FAS activity followed by fructose and, fructose and glucose diet (17 %) when compared to a glucose only meal (8%). But insulin levels are the highest after consumption of the glucose only meal. When the increased levels of lipogenesis followed by a glucose only meal and insulin's cancer triggering effect with its ability to drag large amounts of glucose from the blood for the growth of cancer cells is concerned, glucose appears as an important and effective culprit as much as fructose in the risk of cancer. Also, tumor cells have been reported to disproportionately express high levels of particular form of insulin receptor (IR) (Belfiore and Frasca 2008; Rajapaksha and Forbes 2015). The IR-A isoform of IR might be another reason for the insulin-dependent anti-apoptotic effect of glucose and it is a part of Warburg effect that has often been exploited by tumor cells. Furthermore, the transcriptional regulation of G_6PDH, the rate-limiting enzyme of the Penthose Phosphae Pathway (PPP), in which NADP, NADPH, H2O, ATP and fructose-6-phosphate are produced by Tap73 and Tap63α (the structural homologues of tumor suppressor p53) were described in U2OS osteosarcoma cells (D'Alessandro et al. 2014; Panieri and Santoro 2016). These findings reveal the dual mechanism in cancer once more. First, the apoptotic Tap73 and Tap63α genes are expressed by tumor

cells as well as healthy ones. Second, cancer cells can overexpress G_6DPH which enhances the PPP-dependent production of the apoptotic cofactor, NADPH. Briefly, cancer cells can have apoptotic effect on other cells via Tap73p53 and Tap63p53- regulated G6PDH/NADPH pathway by funneling glucose into the oxidative branch of PPP. In a nutshell, even the tumor suppressors; NADPH, Tap73 and Tap63α, can be exploited by cancer cells as glucose dependent!.

25.c. What happens when the metabolism is deprived of fructose and/or glucose

Glucose and glutamine are utilized by cancer cells via glycolysis to provide carbon skeletons, NADPH (which is essential for nucleic acid and lipid synthesis) and ATP to build new cancer cells in hypoxic micro-environment, 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 similar potentials of both glucose and fructose were 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 cancerogenic potentials of glucose, fructose or galactose and nullity of proposing fructose as the only or most effective culprit of cancer in the current media and literature. More important is that, cancerous cells and several fast-growing cells overexpress P2X7 (purinoreceptor 7), a protein that is encoded by the P2X7 gene in human for extracellular ATP. The 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, cancer cells express the receptor when they face with glucose deprivation. The expression of the receptor also increases the expressions of phosphorylated Akt/PKB and finally hypoxia-inducible factor 1α (HIF-1 α), all of which lead to

the adaptation of cancer cells to glucose deprivation while enhancing the glycogen stores (Amoroso et al. 2012). Under the highlight of all these findings, fructose should be concerned as harmful with its different chemical structure, metabolic intermediates and insulin-independent character. But these attributes can not make fructose as the biggest or most effective culprit while other nutrients; glucose, galactose or glutamine have their own cancerogenic pathways. With or without fructose, each of glucose, galactose or glutamine will continue in their cancerogenic pathways. Needless to point out that glucose, galactose, fructose and glutamine are abundantly exist in foods as combined with important medicinal, essential and anti-cancerogenic bioactive compounds. Therefore, the drawbacks of limiting such foods will have to outweigh its positive incomes.The unnecessarily exaggeration of fructose and glucose deprivation lies in the energy production pathways of cancer cells and healthy cells. Cancer cells exhibit aerobic glycolysis and the rate of glucose metabolism through aerobic glycolysis in cancer cells is higher. When sufficient oxygen is available in both cancer cells and healthy cells, the pyruvate enters the mitochondria where it will be converted to acetyl CoA which enters the citric acid cycle (PPP cycle). In this aerobic glycolysis, the mitochondria produces ≥30 ATP (36-38 ATP yield per molecule) and when insufficient oxygen is present (anaerobic glycolysis), the pyruvates remain in the cytoplasm and undergo fermentation to produce lactate with 2 ATP yield per molecule (Shestov et al. 2014). In conditions of normal oxygen tension, normal cells produce most of their energy via mitochondrial respiration (aerobic glycolysis). In contrast, cancer cells produce over 50 % of their energy in the cytosol via anaerobic glycolysis with the remaining from the mitochondrial respiration (anaerobic glycolysis). So, cancer cells are always exposed to inefficient energy production and therefore they must adopt a mode of increased glucose import to meet their energy demands. As a result, they are expected to switch their energy metabolism from cytosol (anaerobic) to mitochondrial (aerobic) respiration, but they do not. Instead, they overexpress and activate glucose transporters, GLUT1 and GLUT3 and pyruvate kinase (PK) (which regulates the glycolytic flux) and the M-isoform of lactate dehydrogenase while inhibiting pyruvate dehydrogenase complex which

prevents the enterance of pyruvate acid into PPP cycle. The activation of the glycolytic enzymes and inhibition on pyruvate decrease the expression levels of the mitochondrial respiratory complexes I, III and IV, all of which restrict mitochondrial ATP synthesis. The reason for the switch from a high energy production (mitochondrial/aerobic) to a far less energy production (cytosol/anaerobic) might be the protein requirement of cancer cells as a priority when compared with their energy requirement. Amino acid precursors, NADPH and ribose sugars that are the intermediates of anaerobic glycolysis in cytosol, might be a much more preference for cancer cells for their DNA and RNA synthesis (Fadaka et al. 2017). All these important findings reveal the same result. Although sugar intake for energy is important for cancer cells, like for all other living tissues, it is not a priority for them. Even under sufficient oxygen concentrations, they prefer low energy production via anaerobic glycolysis in cytosol to be able to use the intermediates of anaerobic glycolysis for protein synthesis and proliferation. This situation reveals the necessity of interrogating the necessity to limit or reject fructose as the only and biggest culprit for cancer though cancer cells prefer low energy production.

26

DO COHORTS SUPPORT THE ANTI-CANCEROGENIC POTENTIAL OF FOOD BIOACTIVE COMPOUNDS WHICH ARE ALSO EXIST IN FRUCTOSE RICH FRUITS?

When the findings of the cohorts below regarding to the effect of vitamin E on cancer are concerned, the amounts of the subjects in the cohorts which determined the significantly important risk-lowering effect of tocopherol on the risk of cancer are clearly about two times more (2.219.448) than the number of the subjects in the cohorts which determined no effect (1.385.684). Similarly, the number of the cohorts which informed the risk-lowering effect of tocopherol between 1991 and 2014 is far more (26 studies) when compared with the number of the studies which did not determine any effect (12 studies). One of the significant drawbacks of the cohorts is that alcohol or smoking or neither of them was adjusted in 24 studies out of the 38. Additionally, there is no information about the age or the form or the dose of vitamin E in the cohorts of Verhoeven et al. (1997), Bostrick et al. (1993), Do et al. (2003), Jacobs et al. (2002) and Losonczy et al. (1996). In the studies of Eichholzer et al. (2000) and Peters et al. (2008), the combined effect of the vitamin with other vitamins was studied instead of its sole effect. Out of 38, 19 cohorts studied prostate and 8 cohorts studied breast cancer. The types of cancer in other cohorts were lung, pancreas, upper respiratory, colon, liver, gut and ovarian. Unfortunately, the findings of the cohorts about the effects of the vitamin form are conflicted. According to Huang et al. (2003), gamma tocopherol has greater anticancerogenic

effect, while Cui et al. (2014) claim the opposite. Despite the mentioned drawbacks, cohorts clearly indicate a significant anticancerogenic effect of tocopherol, especially on gender-related cancers.

1985-2004 (Stolzenberg-Solomon et al. 2009) →	29.092 men/318 pancreatic cancer/50-69 years of age/smoking adjusted, alcohol not/≥14.2 mg/L (0.59, 0.42-0.83, 95% CI) versus <9.3 mg/L (R:1.00, 95% CI) decreased the incidence rate.
1986-1996 (Chan et al. 1999) →	477 men/754 prostate cancer/40-75 years of age/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.
1985-1988 (Weinstein et al. 2005) →	29133 men/50-69 years of age/smoking adjusted, alcohol not/22 mg/dL (0.49, 0.24-1.01, 95 % CI) versus 14 mg/dL (R:1.00, 95% CI) decreased the risk of prostate cancer.
7.7 years of follow-up (Woodson et al. 1999) →	29.133 men/1144 lung cancer/50-69 years of age/ 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) decreased the risk of lung cancer.
1985-1997 (Hulten et al. 2001) →	27.168 women//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 on the risk of breast cancer.
1993-1996 (Gill et al. 2009) →	96.382 men/467 prostate cancer/45-75 years of age/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.

1992-2000 (Key et al. 2007) →	137.001 men/966 prostate cancer/60 years of medium age/smoking and 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.
1974-1996 (Huang et al. 2003) →	10.456 men/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), and 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) reduced the risk of prostate cancer.
1982-1995 (Gann et al. 1999) →	22.071 men/40-84 years of age/smoking and 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.
5 years of follow up (Cheng et al. 2011) →	18.314 men/778 prostate cancer/smoking adjusted, alcohol not/60.6 years of medium age//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) decreased the risk of prostate cancer.
15 years of follow up (Goodman et al. 2003) →	4060 men asbestos workers, 14254 men heavy smokers/45-69 years of age/alcohol and smoking adjusted/ /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.

6.1 years of follow up (Heinonen et al. 1998) →	29133 men smokers/ /50-69 years of age/ alcohol adjusted and smoking 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.
17 years of follow up (Eichholzer et al. 2000) →	2974 men/87 lung cancer/30 prostate cancer, 28 stomach cancer, 22, colon cancer smoking adjusted, cholesterol adjusted, alcohol not/49-63 years of age/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.
1986-1992 (Zheng et al. 1995) →	41837 women/76 upper respiratory tract cancer/55-69 years of age/smoking and 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.
1984-1993 (Losonczy et al. 1996) →	11178 women/761 ovarian cancer/67-105 years of age/alcohol and smoking adjusted / ≥100 IU/d (0.78, 0.50-1.23, 95% CI) versus no supplementation (R:1.00, 95% CI) decreaed the risk.
3 years of follow up (Do et al. 2003) →	299 women/224 breast cancer/20-69 years of age/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.
8 years of follow up (Knekt et al. 1991) →	36265 men and women/766 various cancers / 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.
1986-1993 (Botterweck et al. 2000) →	120852 men and women/282 gastric carcinoma/55-69 years of age/smoking and alcohol adjusted /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.

1986-1996 (Chan et al. 1999) →	47780 male smokers/1896 smokers with prostate cancer/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.
10 years of follow up (Jacobs et al. 2002) →	991522 men and women/1289 bladder cancer/1982-1998/<40-80≤years of age/ 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.
3 years of follow up (Bohlke et al. 1999) →	1548 women/820 breast cancer/49-61 years of age/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.
8 years of follow up (Hunter et al. 1993) →	89494 women/1439 breast cancer/34-59 years of age/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.
4.3 years of follow up (Verhoeven et al.1997) →	623573 women/650 breast cancer/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.
5 years of follow up (Bostrick et al. 1993) →	167447 women/212 colon cancer/ vitamin E supplementation (0.44, 0.28-0.71, 95% CI) versus no use of supplementation (R:1.00, 95 % CI) decreased the risk.
4 years of follow up (Zhang et al. 2012) →	132837 men and women, 267 with liver cancer, 40-74 years of age/ smoking and alcohol adjusted/>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.
5.8 years of age (Vrieling et al. 2011) →	1295 postmenopausal breast cancer/alcohol and smoking not adjusted 50-74 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.

6.1 years of follow up (Hartman et al. 1998) →	50-69 years of age/317 prostate cancer/ 50 mg/d α-tocopherol supplementation in men with leisure activity (0.7, 0.5-0.9, 95% CI) (RR: 1.0) decreased the risk.
24 years of follow up (Lai et al. 2014) →	29.133 men, 208 liver cancer/smoking adjusted, alcohol not/ 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.
13 years of follow up (Cui 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.
7 years of follow-up (Rodriguez et al. 2004) →	50-74 years of age/ 86.404 men/4281prostate cancer/ smoking adjusted, alcohol not/the highest quintile of vitamin E (≥400 IU/d) (0.96, 0.74-1.24, 95% CI) versus the lowest (R: 1.00) decreased the risk.
10 years of follow up (Peters et al. 2008) →	50-76 years of age/35.242 men/smoking and alcohol adjusted/80 prostate cancer/10 times/ week vitamin E supplementation with the mixture of α, β, ϒ, δ tocopherol (0.16, 0.75-1.1, 95% CI) versus none (R: 1.00, 95% CI) decreased the risk .
5 year of follow-up (Rohan et al. 1993) →	40-59 years of age/56.837 women/519 breast cancer/ smoking and alcohol adjusted /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) decreased the risk.
1985-2004 (Stolzenberg-Solomon et al. 2009) →	29.092 men/318 pancreatic cancer/50-69 years of age/smoking adjusted, alcohol not/≥14.2 mg/L (0.59, 0.42-0.83, 95% CI) versus <9.3 mg/L (R:1.00, 95% CI) decreased the incidence rate.
1985-1988 (Weinstein et al. 2005) →	29133 men/50-69 years of age/smoking adjusted, alcohol not/22 mg/dL (0.49, 0.24-1.01, 95 % CI) versus 14 mg/dL (R:1.00, 95% CI) decreased the risk of prostate cancer .

71985-1997 (Hulten et al. 2001) →	27.168 women//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.
1993-1996 (Gill et al. 2009) →	96.382 men/467 prostate cancer/45-75 years of age/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.
1992-2000 (Key et al. 2007) →	137.001 men/966 prostate cancer/60 years of medium age/smoking and 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.
5 years of follow-up (Goodman et al. 2003) →	18314 men and women/278 lung and 205 prostate cancer/45-74 years of age/ /alcohol and 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.

Table 6. Cohorts which are belong to the effect of vitamin E on cancer.

The very low number of the cohorts below as related to the association of apigenin and cancer risk clearly indicates to a great need for further studies to be able to claim the anticancerogenic effect of the flavonoid.

4 year of follow up (Hoensch et al. 2008) →	160 colon and rectal cancer/alcohol and 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) decreased the recurrence rate of colon neoplasia in patients with resected colon cancer.
11 year of follow up (Gates et al. 2009) →	1183 control/1141 ovarian cancer/52-61 years of age/alcohol and 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.

Table 7. Cohorts belong to the effect of apigenin on cancer

Between 1989-2012, out of 6 cohorts below, only 2 cohorts determined an anticancerogenic effect of the flavonoid, EGCG. In these two cohorts, the number of subjects was musch higher (119746) than the subject number (47759) of the cohorts which did not determine any effect. Though all of the cohorts included the adjustments of alcohol and smoking, the initial drawback of the cohorts is that, all of them studied green tea instead of black or oolong. It is obvious that there is an insufficient number of studies about the association between flavonoid and cancer. Therefore, more cohorts are needed. Due to the low amount of cohort studies, a definite anticancerogenic effect of the flavonoid cannot be claimed.

1990-2004 (Kurahashi et al. 2008) →	50.436 men/404 prostate cancer/alcohol and smoking adjusted/40-69 years of 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.
1991-2001 (Kikuchi et al. 2006) →	26.481 men/110 prostate cancer//40-79 years of age/ smoking and 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.

1965-1986 (Severson et al. 1989) →	5971 men with prostate cancer/smoking and alcohol adjusted/(age adjusted, but not written in the published paper!)/green tea consumption ever (1.47, 0.99-2.19, 95% CI) versus no green tea consumption (R:1.00, 95% CI), did not make any effect.
1970-1972 (Ellison 2000) →	3400 men/145 prostate cancer/50-84 years of age/alcohol and 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.
11 years of follow up (Nechuta et al. 2012) →	69310 women/1255 digestive system(stomach, esophagus, colorectal, liver, pancreas and gallbladder) cancers/smoking and alcohol adjusted/ /≥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.
1975-1994 (Galanis et al. 1998) →	11907 men and women/108 gastric cancer/46-51 years of age/alcohol and 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.

Table 8. Cohorts which are related to the effect of EGCG on cancer

6.3 years of follow up (Schuurman et al. 2002) →	58.279 men, 642 prostate cancer, 55-69 years of age/alcohol and smoking adjusted/≥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.
9 years of follow up (Zhang et al. 2012) →	132.837 women and men, 267 liver cancer, 40-71 years of age/ alcohol and smoking adjusted />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.

6 years of follow up (Daviglus et al. 1996) →	1806 men, 92 prostate cancers/21-96 years of age/ /alcohol adjusted, smoking not/ 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.
30 years of follow up (Berndt et al. 2005) →	1899 men, 132 men with prostate cancer, 40-55 years of age/ alcohol and smoking adjusted/≥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.
10 years of follow up (Pan et al. 2011) →	1496 women with breast cancer with postmenopausal period, 866 women with breast cancer in premenopausal women, 2462 controls, 20-76 years of age/ smoking and alcohol adjusted / 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) decreased the risk.
6.3 years of follow up (Voorrips et al. 2000) →	58.279 men, 939 men with lung cancer, 55-69 years of age/smoking adjusted, alcohol not/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.
6 years of follow up (Kushi et al. 1996) →	34387 postmenopausal women, 879 breast cancer, 55-69 years of age/alcohol and smoking adjusted /≥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.
16.3 year of follow up (Heinen et al. 2012) →	58.279 men, 62.573 women, 566 pancreatic cancers, 55-69 years of age/alcohol and smoking adjusted/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.

1995-1998 (Hutchinson et al. 2011) →	12453 women, 37-79 years of age/alcohol and smoking adjusted/≥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.
6.3 years of follow up (Botterweck et al. 2000) →	3123 men and women, 282 gastric carcinoma, 55-69 years of age/ smoking and alcohol adjusted /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.
10 years of follow up (Jacobs et al. 2002) →	991522 men and women, 1289 bladder cancer/<40-80< years of age/ smoking and alcohol adjusted /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.
1 year of follow up (Do et al. 2003) →	299 women, 272 women with breast cancer, 20-69 years of age/alcohol and smoking adjusted/≥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.
4.1 years of follow up (Nechuta et al. 2011) →	4877 women with breast cancer, 444 deaths, 20-75 years of age/ alcohol and smoking adjusted/Using vitamin C supplement (0,78, 0.63-0.95, 95% CI) versus no vitamin C supplementation (R:1.00, 95% CI) decreased the mortality risk of breast cancer.
6.3 years of follow up (Zeegers et al. 2001) →	3346 men, women, 619 bladder cancer/55-69 years of age/alcohol and smoking adjusted /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) had no effect.

1990-1994 (Hara et al. 2011)	62629 men and women, 40-69 years of age/ alcohol and smoking adjusted/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.
16 years of follow up (Jacobs et al. 2000)	942993 men and women, 596 control, 82345 skin cancer, 30-79 years of age/ smoking adjusted, alcohol not/ /regular vitamin C users (0.83, 0.68-1.01, 95% CI) versus non users (R:1.00, 95% CI) decreased the risk.

Table 9. Cohorts as related to the effect of ascorbic acid on cancer.

In the cohorts above about vitamin C and its association with cancer risk between 1996 and 2011, out of 16 cohorts, only 6 did not observe any effect, though the amount of subjects in these cohorts are slightly more (1.220.371) when compared with the subject number (1.085.504) of the cohorts which determined anticancerogenic effect of the vitamin. Most of the studies (13 out of 16) adjusted the two of the most important cancerogenic factors, 'alcohol' and 'smoking'. Like in tocopherol, the gender origin cancer types, 'prostate' and 'breast', in 8 out of 16 cohorts, were the most studied ones. Opposite vitamin E cohorts, the cohorts about vitamin C and its effect on cancer studied either ascorbic acid or ascorbic acid rich food consumption. Therefore, according to the findings of the mentioned cohorts, a significant anticancerogenic effect of the vitamin can be claimed.

5 years of follow up (Boutron et al. 1996)	171 colorectal cancers, 280 controls/alcohol adjusted/ smoking not 30-75 years of age/ /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.
4 years of follow-up (Bostick et al. 1993)	35.216 women, 216 colon cancers, 55-69 years of age/ alcohol adjusted but smoking not/<127 IU/d (R:1.00, 95% CI) versus >373 IU/d (0.77, 0.55-1.16) decreased the risk.

16 years of follow up (Skinner et al. 2006) →	46.771 men, 75.427 women/38-75 years of age/ smoking adjusted, alcohol not /≥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.
6 years of follow up (Kearney et al. 1996) →	47.935 male, 203 colon cancers, 40-75 years of age/ smoking and alcohol adjusted/>550IU/d (0.42, 0.19-0.91) versus <120 IU/d (0.88, 0.54-1.42) decreased the risk.
9 years of follow up (Zheng et al. 1998) →	34702 women, 1998 rectal cancers, ≥55 years of age/ smoking adjusted, alcohol not />476 IU/d vitamin D intake (0.76, 0.50-1.16) versus <224 IU/d (R:1.00, 95% CI) decreased the risk.
11 years of follow up (Tavani et al. 2005) →	1294 men with prostate cancer, 1451 control, 46-74 years of age/smoking and alcohol adjusted/>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.
1 year of follow up (Jacobs et al. 2007) →	568 men and women, 40-80 years of age/ alcohol adjusted but smoking not/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.
5 years of follow up (McCullough et al. 2003) →	60866 men, 66883 women, 683 colorectal cancers, 50-74 years of age/alcohol and smoking not adjusted /≥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.
1986-2006 (Bao et al. 2010) →	118597 men, 575 pancreatic cancer, 43-70 years of age/ smoking adjusted, alcohol not/>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.

12 years of follow up (Eide et al. 2011) →	3223 men and women with nonmelanoma skin cancer, 55-75 years of age/ alcohol and smoking not adjusted/≥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!.
24 years of follow up (Kilkkinen et al. 2008) →	6937 men and women, 122 lung cancer/36-49 years of age/ smoking and alcohol adjusted / 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.
5.8 years of age (Vrieling et al. 2011) →	1295 postmenopausal breast cancer, 50-74 years of age/ alcohol and smoking not adjusted/≥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.

Table 10. Cohorts about the effect of vitamin D on cancer.

10 cohorts out of 12 cohorts above inform that vitamin D has a significant anticancerogenic effect, especially on colon, colorectal and pancreatic cancers. Most of these cohorts which were held between 1993 and 2011, did not adjust either 'smoking' or 'alcohol' or both, while only 3 of them included the mentioned cancerogenic factors. The number of human subjects in the cohorts which observed the anticancerogenic effect is 420221, while it is only 4517 in the cohorts which claim opposite or no effect. The only unexpected and conflicted results are belong to the cohort of Eide et al. (2011) that, these authors claim the risk- increasing effect of the vitamin. Nevertheless, their results can not be evaluated as definite and reliable since they adjusted neither 'smoking' nor 'alcohol' in their cohort. The most studied cancer forms in these cohorts are colon, colorectal and pancreas. Although a superior number of the cohorts inform the anticancerogenic effect of the vitamin, due to the lack of smoking and alcohol adjustments in most of the cohorts, an

anticancerogenic effect can not definitely be claimed. More cohorts which include the adjustments of the factors 'alcohol' and 'smoking' are needed to make the results of the promising cohorts more reliable.

One of the most crucial and vital missing points about the currently most debated bioactive compound, amygdalin, is the lack of any cohort which analyse its anticancerogenic effect 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 do indicate the inhibitory effects of the glycoside on various cancer signalings and proteins mentioned above, ironically, the compound which is currently in the center of hot debates has not been analyzed by any cohort yet!.

In the cohorts below about lycopene and its relation with cancer risk between 1991 and 2016, out of 9 cohorts, 4 cohorts did not observe any effect. 6 cohorts adjusted the two of the most cancerogenic factors, 'alcohol' and 'smoking'. Like in many other cohorts which studied the association of food bioactive compound and cancer risk, the most studied cancer form was prostate (5 cohorts). Either of lycopene or tomato as the richest source of leukopene was studied in the cohorts. The biggest drawback to be able to claim that lycopene has a reliable anticancerogenic effect is the 'study material'. Tomato is rich in many other anticancerogenic vitamins and flavons like vitamin A, beta carotene and resveratrol besides lycopene. In case of the preference of tomato as a study material, the reason of the anticancerogenic effect can not be determined. Therefore, lycopene itself should have been studied. The numbers of the subjects were closer as 105453 in the 5 cohorts which determined anticancerogenic effect and, 190542 in the 4 cohorts which determined opposite.

9.9 years of follow up (Sesso et al. 2005) →	508 breast cancer/505 control/ /≥45 years of age/ alcohol and smoking adjusted/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.

1986-1992 (Giovannucci et al. 2002) →	47365 men/2481 men with prostate cancer/ smoking and 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.
4.2 years of follow up (Kirsh et al. 2006) →	23631 men and women/55-74 years of age/ smoking and alcohol adjusted/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.
1993-1997 (Lu et al. 2001) →	132 cancer free control/65 men with prostate cancer/smoking and alcohol adjusted//<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.
4 years of follow up (Steinmetz et al. 1993) →	41837 women with lung cancer, 2814 control/ 55-69 years of age/ smoking and 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.
1992-1997 (Wang et al. 2016) →	86402 men/10.864 men with prostate cancer/<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.
6.3 years of follow-up (Schuurman et al. 2002) →	58.279 men/642 men with prostate cancer/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.
1991-1998 (Mayne et al. 2004) →	259 men and women/61 deaths from oral, pharynx and larynx cancers /smoking and 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.

1977-1982 (Fraser et al. 1991) →	34198 adventists/61 lung cancer//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.

Table 11. Cohorts as related to the effect of lycopene on cancer

B_6 and folate appear as the most studied bioactive compounds in the cohorts below. The total number of human subjects in the cohorts, between 1995-2012, which observed anticancerogenic effect is much higher (967989) when compared with the number (162141) of the subjects in the cohorts which claim no effect. Only 2 cohorts did not observe any anticancerogenic effect and 1 cohort claimed the cancer risk increasing effect while 21 cohorts determined an anticancerogenic effect. 21 out of 24 cohorts adjusted the cancerogenic factors 'alcohol' and 'smoking'. Most of the studied cancer forms became colon, rectum and colorectal followed by lung, pancrease, prostate and breast. It can clearly be claimed that B_6 and folate have a significant anticancerogenic effect which is also supported by their inhibitory effects on cancer signalings and proteins, as previously mentioned.

12 years of follow up (Schernhammer et al. 2007) →	121.701 women/30-55 years of age/smoking adjusted and 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.
10.6 years of follow up (Roswall et al. 2010) →	55557 men and women/721 lung cancer/ / smoking and 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!

28 year follow up (Zhang et al. 2012) →	44410 men, 86440 women/alcohol and smoking adjusted/maximum 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.
2000-2006 (Maruti et al. 2009) →	35.023 women/743 breast cancer//50-76 years of age/alcohol adjusted, smoking not/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.
20 years of follow up (Rossi et al. 2006) →	964 men/31 prostate cancer/smoking and alcohol adjusted/>2 µg/L(4.79, 1.56-14.43, 95% CI) folate serum concentration as the highest quartile versus ≤2 µg/L(1.56, 1.05-2.38, 95% CI) as the lowest decreased the risk.
1995-1999 (Gong et al. 2009) →	532 pancreatic cancer, 1701 control/alcohol and smoking adjusted/≥738 µg/d folate supplementation (0.67, 0.48-0.93, 95% CI) versus <280 µg/d (R:1.00, 95% CI) decreased the risk.
2001-2006 (Le Marchand et al. 2009) →	224 colorectal cancer, 411 control, 67.594 men and women/smoking and alcohol adjusted/>26.1 ng/mL plasma folate concentration (0.61, 0.33-1.13, 95% CI) as the highest quartile versus ≤9.94 ng/mL(R:1.00, 95% CI) as the lowest decreased the risk of colorectal cancer.
1980-1994 (Giovannucci et al. 1998) →	442 colon cancer/88756 women/age is not written/smoking and alcohol adjusted/folate (>400 µg/d(0.69, 0.52-0.93, 95% CI) as the highest quartile versus ≤200 µg/d (R:1.00, 95% CI) decreased the risk.
6 year of follow up (Giovannucci et al. 1995) →	47.931 men/ 205 colon cancer/ /smoking and alcohol adjusted/age is not written/>400 µg/d(0.69, 0.52-0.93, 95% CI) versus ≤200 µg/d (R:1.00, 95% CI) decreased the risk.

7.3 years follow up (Konings et al. 2002) →	120852 men and women/760 colon, 411 rectal carcinoma/55-69 years of age/smoking and alcohol adjusted/>266 μg/d folate intake as the highest quartile (0.93, 0.57, 95% CI) versus <168 μg/d as the lowest (R:1.00, 95% CI) decreased the risk of rectal carcinoma, but not colon cancer.
1991-2003 (Ericson et al. 2007) →	11699 women, 392 women breast cancer,1023 colorectal cancer/≥50 years of age/alcohol and smoking adjusted/302 μg/d(0.93, 0.67-1.29, 95% CI) as the highest quartile of folate intake versus 153 μg/d (R:1.00, 95% CI) as the lowest decreased the risk.
1999-2007 (Stevens et al. 2011) →	43512 men and 56011 women with colorectal cancer/50-74 years of age/smoking and alcohol adjusted/≥316 μg/d as the highest quartile of folate intake (0.99, 0.74-1.32, 95% CI) versus the lowest, <198 μg/d (R:1.00, 95% CI) in men and for women (0.86, 0.70-1.06, 95% CI versus R:1.00, 95% CI) decreased the risk.
14.8 year follow up (Larsson et al. 2005) →	61.433 women, 805 colorectal cancer/40-76 years of age/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.
1997-2002 (Van den Donk et al. 2007) →	61433 women/149 colorectal adenoma, 286 control/18-75 years of age/smoking and alcohol adjusted/>183 μg/d (3.25, 0.55-3.22, 95% CI) as the highest quartile versus <183 μg/d (1.04, 0.49-2.22, 95% CI) decreased the risk.
1996-2004 (De Stefani et al. 2008) →	846 lung cancer, 846 control/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.

1992-96 (La Vecchia et al. 2002) →	1225 colon cancer, 728 rectum cancers, 4154 control/smoking and alcohol adjusted/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) as the lowest decreased the risk of colon cancer.
1 year follow up (Theodoratou et al. 2008) →	2500 randomly selected women /smoking and alcohol adjusted/25-74 years of age/low serum folat concentration (<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 of colorectal cancer.
1993-2001 (Stolzenberg-Solomon et al. 2006) →	25400 women, 691 breast cancer/55-74 years of age/alcohol and 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.
1988-1992 (Glynn et al. 1996) →	144 colon and rectum cancer, 276 control/50-69 years of age/alcohol and 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.
1986-1998 (Harnack et al. 2002) →	41836 men and women/55-69 years of age/598 colon, 123 rectal cancer/alcohol and smoking adjusted/≥634 (1.12, 0.77-1.63, 95% CI) folate intake as THA highest quartile versus ≤231 µg/d (R:1.00, 95% CI) the lowest highest quartile decreased the risk of colon cancer.
1995-2002 (Ishihara et al. 2007) →	81184 men, 526 colorectal cancer/48-53 years of age/smoking and alcohol adjusted/246 g/d folate as the lowest quartile of folate intake (R:1.00, 95% CI) versus 461 g/d (0.93, 0.56-1.54, 95% CI) as the highest and 1.75 mg/d (R:1.00, 95% CI) B_6 as the lowest (R:1.00, 95% CI) versus 5.2 mg/d (0.69, 0.41-1.14, 95% CI) as the highest did not make any effect on the risk of colorectal cancer.

1985-1988 (Weinstein et al. 2008) →	29133 men/50-69 years of age//152 colon cancers and 126 rectal cancers, 1371 control/ smoking and alcohol adjusted/77.7 pmol/ mL plasma B_6 concentration (0.91,0.35-2.42,95%CI) as the highest quartile versus12.7 pmol/mL (R:1.00, 95% CI) as the lowest quartile decreased the risk.
16 year follow up (Zhang et al. 1999) →	3483 breast cancer/smoking and alcohol adjusted/30-55 years of age/≥600 μg/d folat intake (0.91, 0.82-1.01, 95% CI) as the highest versus <150 μg/d (1.09, 0.89-1.32, 95% CI) decreased the risk.
1989-1996 (Zhang et al. 2003) →	712 breast cancer, 32826 women/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.

Table 12. Cohorts which are related to the effect of folate and B_6 on cancer.

The cohorts below about quercetin and its association with various cancer types until now took place in the period between 2001 and 2010. In these cohorts, only 3 out of 10 did not observe any effect of the flavonoid. Except the one belongs to Knekt et al. (2002), all other cohorts adjusted both 'alcohol' and 'smoking'. The total number of the subjects in the cohorts, which claimed the anticancerogenic effect is 398450 which is higher than the subject number (201014) in the cohorts which claimed opposite. Particularly, the findings of Wilson et al. (2009) are important since they indicate to the risk-minimizing effect of the flavonoid in male smokers. One of the drawbacks of the cohorts which belongs to Lam et al. (2010) and Lin et al. (2006) is the absence of the quartiles. Also, the findings of Hirvonen et al. (2001) can not be attributed to only quercetin since the authors studied the intakes of total flavonol and flavones including quercetin. But overall, a significant anticancerogenic potential of the flavonoid can be claimed.

1993-2002 (Nöthlings et al. 2007) →	183.518 men and women/529 pancreas cancer//45-75 years of age/smoking and 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.
1966-1972 (Knekt et al. 2002) →	62440 men and women//39.3±15.8 years of median age/smoking adjusted, alcohol not/3.6 mg/d (0.88, 0.78-1.00, 95% CI) as the highest quartile of quercetin intake versus 2.7 mg/d (R:1.00, 95% CI) as the lowest quartile decreased the risk in lung cancer.
1985-2002 (Wilson et al. 2009) →	27111 men/228 renal cancer/50-69 years of age/alcohol and smoking adjusted/>9.1 mg/d (0.7, 0.5-1.0, 95% CI) as the highest quartile versus ≤4.8 mg/d (R:1.00, 95% CI) decreased the risk in male smokers.
1984-2002 (Gates et al. 2007) →	66.940 women/347 ovarian cancer/30-55 years of age/ smoking and alcohol adjusted/30.7 mg/d (0.80, 0.55-1.16, 95% CI) as the highest quartile versus 6.3 mg/d (R: 1.00, 95% CI) as the lowest quartile decreased the risk.
1985-2004 (Bobe et al. 2008) →	27111 male/306 pancreatic cancer/50-69 years of age/smoking and alcohol adjusted />9.87 mg/d (1.07, 0.75-1.53, 95% CI) as the highest quartile versus ≤4.44 mg/d (R: 1.00, 95% CI) as the lowest decreased the risk.
11.5 years of follow up (Wang et al. 2009) →	38.408 women/3234 breast, colorectal, lung, endometrial and ovarian cancers/ /≥45 years of age/alcohol and smoking adjusted/32.79 mg/d (0.91, 0.81-1.01, 95% CI) as the highest quartile versus 6.49 mg/d (R: 1.00, 95% CI) as the lowest did not make any effect.
8 years of follow up (Adebamovo et al. 2005) →	90630 women/710 breast cancer/smoking and alcohol adjusted/26-46 years of age/30.1 mg/d (1.05, 0.85- 1.33, 95% CI) as the highest quartile versus 5.3 mg/d (R: 1.00, 95% CI) as the lowest did not make any effect.

1990-1998 (Lin et al. 2006)	71.976 women and 35425 men/878 colorectal cancer/30-55 years of age//smoking and 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.
2002-2005 (Lam et al. 2010)	2120 control, 2100 lung cancer/64.8-66.3 years of median age/smoking and 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.
6.1 years of follow up (Hirvonen et al. 2001)	27110 male smokers/791 lung, 226 prostate, 156 urothelial, 111 stomach, 133 colorectal, 92 renal cancer/50-69 years of age/alcohol and 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.

Table 13. Cohorts about the effect of quercetin on cancer

Between 1990 and 2015, 7 out of 12 cohorts below, did not observe any effect of the provitamin, β-carotene, while some of them even claimed the cancer risk increasing potential of the provitamin. Only one among the cohorts did not adjust 'smoking' and 'alcohol'. The number of the subjects in the cohorts which claim the protective effect of the provitamin is 244338, while the number is 199001 in the cohorts which claim the opposite. In spite of the higher number of subject and the claims which indicated to the anticancerogenic potential of the provitamin, there are very important drawbacks of these cohorts. Though lung cancer is not gender-based cancer, Rohan et al. (2002) studied only women. The amount of the beta carotene supplementation is not mentioned in the cohort of Kamangar et al. (2006). The unexpected risk increasing effect in both cohorts of the provitamin is due to the study material which was consisted of smokers. The reason for the unexpected findings might be the chemical quenching of the singlet oxygen by carotenoids (Ramel et al. 2012). These results are vitally important since they indicate the higher risk potential of beta carotene supplementation particularly

in smokers, by quenching single oxygen atom by nicotine in smoke and creating a far greater hypoxic micro-environment media which trigger the growth of cancer cells. Although the risk of the provitamin in smokers is an important detail, the pro-vitamin cannot be blamed for cancer in healthy individuals. On the other hand, the results of the cohorts of Holick et al. (2002) and Dartigues et al. (1990) which claim the protective potential of the provitamin might be due to the higher doses, >290 μg/L and 7226 IU/d, respectively. Therefore, the provitamin might have an anticancerogenic potential provided that its dose is >290 μg/L or 7226 IU/d. Otherwise, it should be carefully considered that beta carotene supplementation, when combined with smoking!, may be harmful because of its oxygen quenching potential. With all the mentioned limited data and 7 cohorts which did not observe any effect, it is very clear that more researches are needed to be able to claim a definite and reliable anticancerogenic potential of the provitamin.

1980-1993 (Rohan et al. 2002) →	5681 women, 155 lung cancer/40-59 years of age/smoking and 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.
1986-1991 (Kamangar et al. 2006) →	29584 men and women, 147 lung cancer/40-69 years of age/smoking and alcohol adjusted/ daily beta carotene supplementation (0.55, 0.26-2.14, 95% CI) decreased the risk in 31 lung cancer, versus no supplementation (R:1.00, 95% CI).
6.2 years of follow-up (Omenn et al. 1996) →	18314 men and women/Smoking, asbestos and 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!

7.4 years of follow up (Touvier et al. 2005) →	59910 women/40-65 years of age/ smoking and 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.
1985-1993 (Malila et al. 2002) →	29133 men/50-69 years of age/ 27084 male smokers, 1644 lung cancer, 126 gastric cancer, 75 intestinal cancer/smoking and alcohol adjusted/20 mg/d beta carotene supplementation (0.88-1.80, 95% CI) versus no supplementation (R:1.00, 95% CI) increased the risk of intestinal cancer while it has no effect on the other cancer forms.
14 years of follow up (Holick et al. 2002) →	27084 male smokers/ 50-69 years of age/smoking and 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.
7.7 years of follow up (Woodson et al. 1999) →	1059 lung cancer, 27111 men/smoking and 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.
1983-1984 (Dartigues et al. 1990) →	106 epidermoid lung cancer, 212 controls/ Smoking and 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.
24 years of follow up (Lai et al. 2014) →	29105 men/smoking and 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.
20 years of follow up (Eliassen et al. 2015) →	32826 women, 2188 breast cancer/43-69 years of age/smoking and 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.

4.3 years of follow up (Verhoeven et al. 1997) →	62573 women, 650 breast cancer/alcohol adjusted, smoking not/55-69 years of age/0.719 mg/d as the highest (1.01, 0.72-1.42, 95% CI) versus 0.197 mg/d (R:1.00, 95% CI) as the lowest quartile did not make any change.
1980-1998 (Tamimi et al. 2005) →	121700 women, 969 breast cancer/30-55 years of age/smoking and alcohol adjusted/1.15 μmol/L (0.53-1.02, 0.73, 95% CI) versus 1.03 μmol/L (R:1.00, 95% CI) as the lowest decreased the risk.

Table 14. Cohorts which are related to the effect of β-caroten on cancer.

One of the most important antioxidant flavonoids, resveratrol, has a very limited number of cohorts though many studies approve its anticancerogenic effects on cancerogenic proteins and signalings. In one of these cohorts, 1270 men and women were studied during 6 year follow up as smoking and alcohol adjusted. No association was observed when the highest quartile of resveratrol metabolites (nmoL/g creatinine) (0.51, 6.69-7.29, 95% Cl) was compared with the lowest (0.08, 1.51-2.29, 95% Cl) (Semba et al. 2014). The main drawback of the cohort is that it studied one of resveratrol's metabolites, creatinine, instead of studying resveratrol directly. Furthermore, creatinine is not the metabolite of only resveratrol, but also several drugs such as cimetidine, trimethoprim, corticosteroids, pyrimethamine, phenacemide, salicylates and vitamin D (Andreev et al. 1999). A limited number of other studies about 'resveratrol and cancer' is reviews and case-control studies which used animal subjects as study material. Also, the studies which are included in a very limited number of reviews are case-control rather than cohort. A clear example is the review of Carter et al. (2014) in which all the reviewed studies are case-control with animal subjects. Similarly, sulforaphane has got the same drawback with resveratrol and beta carotene to be able to claim its anticancerogenic effect. All of the 41 cohorts in the review of Tortorella et al. (2015) use cruciferous vegetable weekly consumption rates as the main objective and indicator of the flavonoid. The anticancerogenic effect in all these cohorts cannot be attributed to only sulforaphane since green leafy and cruciferous

vegetables are also rich in many other anticancerogenic food bioactive compounds such as Zn, Mg, folate, lutein, beta carotene, ascorbic acid, vitamins E, K and A, soluble fiber, folic acid, omega-3 PUFAs, nitrate and retinol (Pollock et al. 2016). Similarly, the cohorts belong to Alumkal et al. (2015), Traka et al. (2008) and Egner et al. (2011) studied sulforaphane rich food, broccoli, rather than studying sulforaphane. In the study of Cipolla et al. (2015), 78 men (69±6 years of age) with prostate cancer were given 60 mg sulforaphane orally for 6 months while smoking and alcohol were not adjusted. The treatment decreased the elevated PSA levels. In spite of the case-control studies which use animal subjects, and a few cohorts which have drawbacks and claim the anticancerogenic potentials of both vitamins, sulforaphane, and resveratrol, it is clear that more reliable cohorts with human subjects are needed. It is uppermost important that adjustments of factors including alcohol, smoking, and gender should not be neglected in such cohorts.

27

WHEN IT COMES TO PROBIOTIC AND CHEMOTHERAPY INTERACTION

The beneficial effects of probiotics have often been described in allergic sensitization and diseases, but cancer prevention by probiotic might be a promising target for anticancer treatments. Confirmingly, the most effective anti-allergic strain, *Bacillus coagulans* 09.712 (Bc) (10^9 cfu/100 µL sterile phosphate-buffered saline, PBS/d for 35 d) (Fu et al. 2017) greatly improves epithelial barrier function and increases lymphocyte proliferation. It also induces CD4+/Foxp3/Tregs pathway while suppressing Th17 proinflammatory response and altering Th1/Th2/Treg balance (Figure 8). The other probiotics for the induction of the CD4+/ Foxp3/Tregs pathway are *L. plantarum*, *B.infantis*, *S. thermophilus*, *L. rhamnosus*. The suppression of the Th17 proinflammatory cytokine and the induction of the pathway, CD4+/Foxp3+/Tregs, might have a beneficial effect by improving the adaptation and self-defence attributes of the healthy cells while protecting them from inflammation. But, expectedly, if the approach in the anticancer treatment is the inhibition of CD4+ and Foxp3, to eliminate the risk of 'data copying and transfer' of cancer cells from CD4+ T cells and boosting their defence system by exploiting Foxp3, then any probiotic or probiotic combination or probiotic rich nutrition like fermented meat, fermented dairy products and pickled products might have been contraindicated with the CD4+ T inhibitors and CD4+ T cell inhibiting food/plant bioactive compounds. Under the highlight of the latest findings, such foods might only be beneficial in a healthy individual who does not take any anti-cancer

treatment which administers the inhibition of CD4+ T cells. Probiotics or probiotic rich foods might only be beneficial in people without cancer by boosting CDT cell proliferation and activity while it might be harmful and contraindicated in individuals with cancer who are prescribed with CDT inhibitors. Opposite to the treatments which target CDT cell inhibition, if the chemotherapeutic agents are COX-2 inhibitors, then the patient might benefit from probiotic and probiotic rich nutrition. Confirmingly, *Lactobacillus acidophilus* (10^6 cfu/mL,10mL per well, pH: 6.8/24h treatment in the colon cancer cell lines; Colo320 and SW480) was informed to inhibit the expression of the pro-inflammatory enzyme (Otte et al. 2009).

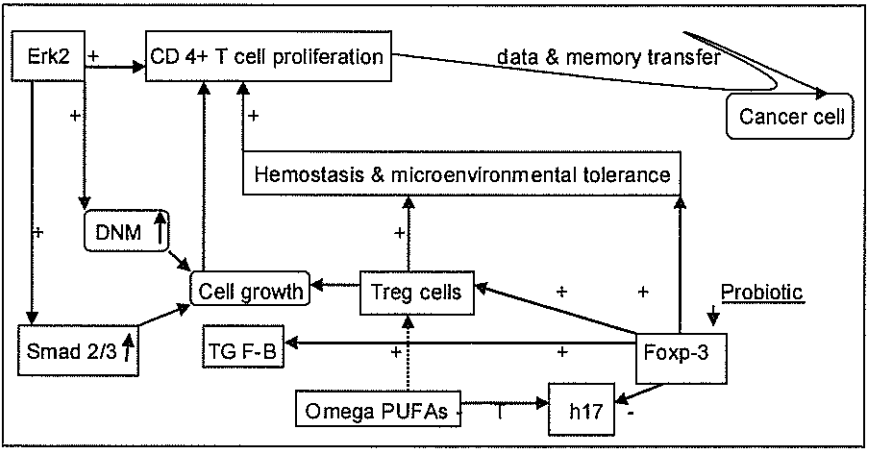


Figure 8. Erk/Smad/TGF-B/Foxp-3 and CD4+ T cell interactions

The probiotic supplementation or probiotic rich food consumption is not only important during treatment, but also for the protection from cancer progress or the side effects of some anti-cancer treatments like radiotherapy. The administration of $5x10^7$ *Lactobacillus rhamnosus* GG (LGG)/3d before 12 Gy whole body radiation to 8-week-old C57BL/6 (inbred strain, produced by a minimum of 20 generations of brother-sister mating) was found not to change COX-2 levels as conflicted with the findings of Otte et al. (2009), but this administration resulted in repositioning of COX-2-expressing mesenchymal stem cells of the lamina propria from the villi to the crypt region (Ciorba et al. 2012). So, the orally probiotic supplementation causes less injury on lamina

propria of intestinal epithelium which is caused by COX-2 induction by radiation. The translocation of COX-2-expressing mesenchymal stem cells to the lamina propria from villi limits the injury on the lamina propria which produces COX-2 and lessens the risk of the side effect, the radiation-induced diarrhea from colorectal small bowel epithelial injury. The treatment of HT-29 human mucus secreting adenocarcinoma cell line for 18h with one of the following probiotics (50 μL/10^8 cfu/mL); *Lactobacillus acidophilus*, *Saccharomyces boulardii*, *Lactobacillus lactis*, *Lactobacillus casei* and *Lactobacillus reuteri,* inhibits pro-inflammatory and pro-cancerogenic cytokines; PGE-2, IL-8, IL-1β, IL-6, TNF-α, and IL-10 (De Marco et al. 2018). Finally, the probiotic yeast, *Saccharomyces boulardii* inhibits VEGFR, the vascular endothelial growth factor receptor and regulator of angiogenesis (Chen et al. 2013). Besides, the probiotic (6x 10^8 cfu/d for 5d oral administration to mice) has a significant protection against intestinal injury and inflammation.

IFN-ϒ was first known with its dual effect like many other molecules and proteins in cancer. It stimulates the expression of major histocompatibility complex (MHC) molecules to increase immunogenicity of tumor cells and makes them more susceptible to immune recognition and destruction. They also display anticancer activity via the inhibition of cell proliferation, e.g. by upregulating p21 and p27 molecules to arrest cell cycle (Martini et al. 2010; Chawla-Sarkar et al. 2003). Unfortunately, the protein has a dark side besides its well-known anti-cancerogenic effect. It upregulates MHC molecules on tumor cells and decrease their sensitivity to the Natural Killer cells (some of the T and B cells) (Taniguchi et al. 1987). The pleiotropic cytokine also increases the expression of several markers, e.g. HLA-DR (leucocyte antigen) and ICAM-1 (intracellular adhesion molecule) in advanced melanomas (Garbe et al. 1990). On the other hand, *Lactococcus lactis subsp. Cremoris* FC (10^9 cfu in saline, orally administered to mice for 2 consecutive days) enhances the production levels of IFN-ϒ and IL-10 (Kosaka et al. 2012). Like IFN-ϒ, the cytokine has dual effect as in close interaction with IFN-ϒ is IL-22. Its protective effect might be due to the poorly defined changes in epithelial cell transcriptional circuitry that protect against tissue damage while promoting tissue

repair and fostering probiotics, all of which may result in the prevention of excessive inflammation (Hernandez et al. 2017). The approaches which target the inhibition of the cytokine, except the advanced stages of cancer like in advanced melanomas, may severe the prognose. A clear example might be the correlation between the limited presence of IL-22 binding protein (IL-22BP), a natural IL-22 inhibitor and strenghthening of psoriatic skin inflammation (Martin et al. 2017). The findings of Lin et al. (2017) indicate that the treatment of Colo 205 cells with the probiotic, *Lactobacillus paracasei* BL23 (pH: 6.0, 2mL/10^9 cfu/mL in 6-well plates of Colo 205 cells, incubated at 35 °C/22h), might potentially be useful at this point as a mucosal therapeutic agent by decreasing the rate of inflammation in IL-22 origin. Briefly, probiotics have several anticancerogenic effects, but like in all other food/plant bioactive compounds, their intakes should have been regulated as specific to the type of chemotherapy.

28

N-3 OMEGA FATTY ACIDS, THEIR ASSOCIATION WITH THE CANCEROGENIC PATHWAYS AND CHEMOTHERAPY

Increased concentrations of eicosanopentaenoic acid as one the main constituents of n-3 omega polyunsaturated fatty acids (n-3 Omega PUFAs) protect against colorectal and pancreatic cancer while decreasing tumour size (Nkondjock et al. 2003; Barber et al. 1999 and Gogos et al. 1998). Moreover, fish oil, alone or as combined with soy bean, produces 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 (3g/Kg/d) is not only effective as an antitumour agent, but also they mediate the effects of nutritional interventions by prolonging life span, suppressing autoimmune diseases (Troyer and Fernandes, 1996) and triggering the expression of tumour necrosis factor (Gomaa and Abd El-Aziz 2016). Unlike the significant protective and suppressing effects of n-3 omega PUFAs in cancer and autoimmune diseases, n-6 omega PUFAs increase cancerogenic eicosonoids and the risk of tumour progress (Huerta-Yepez et al. 2016). In contrast, 3 g daily supplement of flaxseed, a rich source of lignan and n-3 omega PUFAs, decrease the prostate specific antigen levels (PSA) and lowers the rate of proliferation (Demark-Wahnefried et al. 2001). On the other hand, 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 the consumption rate of omega 3 fatty acids, not only to prevent the risk of

cardiovascular disease, but also maintain weight balance. The protective effect of n-3 omega PUFAs against cancer is mainly determined by the following factors: the type of cancer, metabolism, genes, sex, age and diet. Whereas n-3 omega PUFAs show their protective effect against cancer by acting on metabolism, high intakes of dietary n-6 Omega PUFAs, e.g linoleic acid, can elevate oestrogen levels in pregnancy, altering mammary gland morphology and expression of fat-and/or oestrogen-regulated genes, all of which leads to the risk of breast cancer (Clarke et al. 1999). In contrast, supplementing the diet of tumour-bearing mice with n-3 omega PUFAs was claimed to slow the progress of various cancer types including lung, colon, mammary and prostate with a remarkable improvement in the efficacy of cancer chemotherapy drugs such as doxorubicin, epirubicin, 5-fluorouracil, tamoxifen and of radiation therapy (Hardman 2004).

28.a. MAPK/ERK pathway, AP-1 and their relation with the food/plant bioactive compounds and Omega 3 PUFAs

Omega 3 PUFAs (EPA, 20 μg/mL and DHA, 20 20 μg/mL) inhibits the transcription activator protein 1 (AP-1), a protein which is responsible for gene expressions that cause cell proliferation and tumour formation in mouse epidermal JB6 P+1-1 cells, (Liu et al. 2001). So, currently the most common AP-1 inhibitors; SR 11302 (E, E, Z, E)-3-Methyl-7-(4-methylphenyl)-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonatetraenoic acid (Mishra and Kim 2017; Gonzales-Rubio et al. 2016), Heat Shock Transcription Fator, HSF1 (Sawai et al. 2013), SP 100030 (N-[3,5-Bis(trifluoromethyl)phenyl]-2-chloro-4-(trifluoromethyl)5-pyrimidinecarboxamide) (Moore-Carrasco et al. 2007), tanshinone IIA (6, 7, 8, 9-tetrahydro-1, 6, 6-trimethylphenanthro [1,2-b] furan 10,11-dione (Jin et al. 2008), sunitinib (Zhang et al. 2014) and bortezomib (Lauricella et al. 2006), might benefit from Omega 3 PUFAs rich nutrition or EPA&DHA supplementations or the combinations with the following food bioactive compounds which similarly inhibit AP-1; sulforaphane (2.5 μM/25 g weight, 3 times/w in rats) (Dickinson et al. 2009), beta carotene (10 μM/2h in the preadipocyte cell line, 3T3-L1) (Cho et al.

2018), alpha tocopherol (100 μM/15 min. in rabit peritoneal and human macrophages) (Teupser et al. 1999), lycopene (10 μM/30 min. in rat microglia cells) (Lin et al. 2014), genistein (370 μM/72h in the human epidermal keratinocyte cell culture, Nhek) (Jurzak and Adamczyk et al. 2013), vitamin D3 (400 nM/72h, in the breast cancer cell line, MCF-7) (Voigt 2006), apigenin (100 μM/24 h, in the human lung alveolar type II epithelial cell line, A549) (Patil et al. 2016), ascorbic acid (5μM/5h, in the human keratinocyte cell line, HaCaT)(Catani et al. 2001) and EGCG (30 μM/24h, in the human gastric carcinoma cell line, AGS) (Kim et al. 2004). The mentioned AP-1 inhibitors and food bioactive compounds including Omega 3 PUFAs might create a synergism for a much greater inhibition on AP-1. On the other hand, resveratrol (20 μM/24 h) in the hepatoma cell line, HepG2 and the kidney cell line, HEK293) (Thiel and Rössler 2014), arginine (50 μM//120 min, in human mesangial kidney cells) (Ruiz-Torres 2007) and quercetin (50 μM/1080 min., in human hepatoma cell line, HepG2) (Granado-Serrano et al. 2010) with their inducing effect on AP-1, should better be avoided in such anti-cancer treatments which target AP-1. Finally, the effect of folic acid, folat, B_6 and I3C on the factor is still waiting to be highlighted.

The 'syndecans' which are consisted of four transmembrane heparin sulfate proteoglycans (HSPGs) on the cell surface are involved in 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, and the anti-apoptotic protein, 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 and inducing syndecan; synstatin (Rapraeger et al. 2013), the organic and inorganic hybrid molecules e.g., O-Phen, Zn-Phen, Rh-Phen (in 1,10-phenanthroline structure which are exist naturally in vascular endothelial cells) (Hara et al. 2017), varinostat, ritonavir, radicicol, tamoxifen, geldanamycin, lapatinib, fulvestrant, PD98059, UO126, honokiol and SNX212, might benefit from the combination with Omega 3 PUFA rich nutrition or supplementation by creating a synergy via the up-regulation of Syndecan-1 and inhibition of

MAPK/ERK signaling. Nevertheless, there is currently no study about the relation of syndecan and any food bioactive compound, except the one belong to Strunz et al. (2017) which informs the inducing effect of resveratrol (22.04 mg/Kg/d for week supplementation in rats and 50 μM serum concentration) on Syndecan-1.

28.b. The effects of the food/plant bioactive compounds and Omega 3 PUFAs on Bcl- Bax, Bim and Wnt/B-catenin

BimEL, a member of Bim pro-apoptotic proteins, is controlled by ERK1/2 mediated phosphorylation which targets BimEL for ubiquitination and degradation. TGFβ, the transforming growth factor-β signaling, induces the expression of Bim by phosphorylating receptor-regulated SMADs (Ramesh et al. 2009) which act as transcription factors, leading to the up-regulation of β-lymphocyte expression. On the other hand, DHA (200 μmol/L/72h, in the immortalized human hepatocellular carcinoma cell line, Bel-7402) up-regulates the expression of the apoptotic protein, Bax, activates the apoptotic enzymes, Caspases, while inhibiting the expression of the anti-apoptotic proteins, Bcl-2 and Bim (Sun et al. 2013). Therefore, the Bax inducing and Bcl-2/Bim inhibiting drug administrations might benefit from Omega 3 PUFAs and the food/ pland bioactive compounds. That Omega 3 PUFAs increase the expression levels of TGF-β and SMAD (150 μM/72h in the ovarian cancer cell lines; SKOV-3 and OVCAR-3) (Sharma et al. 2009), might be one of the most remarkable anti-cancerogenic effects of the fatty acids. Additionally, Docosahexaenoic acid (DHA), one of the two main components of Omega 3-PUFAs, has been informed to inhibit the anti-apoptotic signaling, Wnt/β-catenin (Park and Kim 2017). Confirmingly, 50 μM/24h EPA+DHA treatment of the pancreatic cancer cell line, PANC-1, and 30 μM/24h DHA+EPA treatment of the pancreatic cancer cell line, SW1990, have a significant inhibitory effect on Wnt/β-catenin signaling (Song et al. 2011). Wnt and beta catenin inhibitors are as follows; niclosamide (Zhao et al. 2016), sunitinib (Yang et al. 2017), metformin (Melnik et al. 2018), tetrandrine (TET, 6, 6',7,12-tetramethoxy-2,2'-dimethyl-1 β-berbaman, a bisbenzylisoquinoline alkaloid purified from

the root of *Stephania tetrandra*) (120 μM/48h, in the human colon cancer cell line; HCT116 and breast cancer cell line, MDA-MB-231) (He et al. 2011), oxospiramilactone (a diterpene from family Spiraea, 7.5 μM/17h, in the colon cancer cell lines; HEK293T, SW480 and Caco-2) (Wang et al. 2011), aesculetin (a natural coumarin compound, 2.24 μmol/L/72 h, in the colon cancer cell line; SW480) (Li et al. 2018), lupeol (a dietary triterpene in olives, mangoes, grapes and figs, vegetables, e.g., green peppers and *Aloe vera* (40 mM/48 h, in the colorectal cancer cell lines; DLD1 and HCT 116) (Tarapore et al. 2013), lapatinib (Yao et al. 2017), deguelin (a rotenoid, naturally occurring substance containing a cis-fused tetrahydrochromono [3,4-b]chromone nucleus with intestinal activity, 1 mumol/L/72 h, in the breast cancer cell lines; MDA-MB-231, MCF-7, BT474, T47D, and human mammary epithelial cell line, MCF12F) (Murillo et al. 2009), tunicamycin (Li et al. 2018), tautomycin (Kim et al. 2013), p38 MAPK (SB203580) (Bikkavilli et al. 2008), SMO04690 (a small molecule) (Deshmukh et al. 2018), gigantol (a novel Wnt/β-catenin inhibitor and bibenzyl compound derived from medicinal orchids, 100 μM/24h in breast cancer cell lines; MDA-MB-468, MDA-M-231) (Yu et al. 2018), Scaffold/ Matrix Attachment Region Binding Protein1 (SMAR1) (Taye et al. 2018), NCTO1973309 (a monoclonal antibody), paclitaxel (Pai et al. 2017), honokiol (Singh and Katiyar 2013), Scaffold/Matrix Attachment Region Binding Protein1 (SMAR1) (Taye et al. 2018), tankyrases 1,2 (Chen et al. 2009), PP2A phosphatase (Yamamoto et al. 1999), p38 MAPK (Thornton et al. 2008), Sox9 (an intrinsic transcription factor) (Topol et al. 2009), arginine (100 μM/48h, in mesenchymal stem cells while it also activates Wnt5a) (Huh et al. 2014), genistein (25 μM/72h, in the renal cancer cell lines; A-498, HTB-44, CRL-1932, Caki-2 and HTB-47) (Hirata et al. 2013), quinacrine (an antimalarial drug and antibiotic) (Preet et al. 2013), sulforaphane (16 μM/48h, in the breast cancer cell lines, SUM159, MCF7) (Li et al. 2010), folic acid (in zebra fish fertilized egg cells, but the study is invivo and supplementation dose is not exist in the published paper) (Yue et al. 2017), tetrandrine (bisbenzylisoquinoline alkaloid) (He et al. 2011), niclosamide (a drug used for the treatment of tapeworm) (Chen et al. 2009), ottogi (a protein in zebrafish embryos) (Kim et al. 2017), SR 141716 (a cannabinoid

that acts on cannabinoid receptors in cells that alter neurotransmitter release in the brain) (Proto et al. 2017), ascorbic acid (100 μM/24h, in the human neural progenitor ReNcell VM cells) (Rharass et al. 2017), apigenin (60 μM/20h, in P19-embryonic carcinoma cells) (Lin et al. 2017), vitamin D_3 (1000 nM/48h, in the human uterine fibroid cells, HuLM) (Al-Hendy et al. 2016), I3C (300 μM/24h, in the human prostate carcinoma cell line; DU145) (Jeong et al. 2011), resveratrol (40μg/mL/96h, in the human osteosarcoma cell line, MG-63) (Zou et al. 2015), quercetin (60 mM/80h, in the prostate cancer cell line, PC-3) (Baruah et al. 2016), EGCG (60 μM/48h, in the human colon cancer cell lines, DLD-1 and SW480) (Chen et al. 2017), nitazoxanide (an antiparasitic drug) (Qu et al. 2018), SR141716 (a cannabinoid that acts on cannabinoid receptors in cells that alter neurotransmitter release in the brain) (Proto et al. 2017), IWP-2 (CAS686770-61-6) ($C_{22}H_{18}N_4O_2S_3$) (Mo et al. 2013), PNU-74654 ($C_{19}H_{16}N_2O_3$) (Leal et al. 2015), IWR-1-endo ($C_{25}H_{19}N_3O_3$) (Chen et al. 2009), demethoxy curcumin ($C_{20}H_{18}O_5$) (40 μM/15h, in the human embryonic kidney cell line; HEK293) (Ryu et al. 2008), KYO2111 ($C_{18}H_{17}ClN_2O_3S$) (Minami et al. 2012), kaempferol (30 μM/24 h, in the human retinoblastoma cell line, S0-RB50) (Qin et al. 2016), jatrophone (the diterpene isolated from *Jatropha gossypiifolia*, 100μM/24h, in the breast cancer cell lines; MDA-MB-231, HCC38, MDA-MB-157 and MDAMB-468, human osteosarcoma cell lines; U20S and MG3 and cervical cancer cell line, HeLa) (Fatima et al. 2017), *Ganoderma lucidum* (medicinal mushroom as derived from ethanol extraction, 200 μg/mL/48h, in the human embryonic kidney epithelial cell lines; HEK293T and HEK293FT, human breast cancer cell line, MDA-MB-231 and mouse breast cancer cell line, 4T1) (Zhang 2017). All these agents and bioactive compounds might benefit from Omega 3 PUFAs rich nutrition or supplementation via the synergism to create a much stronger inhibition of Wnt/β-catenin signaling.

Omega 3 PUFAs (DHA or EPA, 100 μM/24h, in the human umbilical vein endothelial cells, HUVEC) inhibit the over-expression of inflammatory COX-2 and NF-kB (Lee et al. 2009). Therefore, the chemotherapeutic agents and food/plant bioactive compounds which target cancer cells by inhibiting COX-2 and NF-kB, e.g., I3C, apigenin,

kaempferol may benefit from Omega 3 PUFAs rich nutrition or their supplements via the inhibition of the pro-inflammatory enzyme and the gene which may lead to a better prognosis in cancer treatments. The most important and remarkable point among the latest findings is the specific anti-cancerogenic effect of DHA (200 μM/48h, in the breast cancer cell lines, MDA-MB-231 and 4T1) by inducing ROS, caspase activity and activating IL1B (a proinflammatory cytokine which promotes the stemness and invasiveness of cancer cells), while DHA does not affect healthy cells (Pizato et al. 2018). The inhibition of IL1B prevents blood vessel formation which is induced by products of hypoxic macrophages, inhibits the growth of vascular endothelial cells and subsequently inhibits metastasis (Dinarello 2010). But, the induction of the cytokine may create a media to gather the cancer cells and bind them into the walls of vessels, exposing them to the effect of ROS which are produced by the fatty acids. At this point, it should be significantly noted that the fatty acids and also I3C (1 mM748h, in the human monocytic cell line, THP-1) (Mohammadi et al. 2017), vitamin D (1.25D(+D), 100 nM/24h, in the human monoctic cell line, THP-1) (Verway et al. 2013) and their rich sources or supplementations, all of which induce IL-1β, might be contraindicated if the chemotherapeutic agents which are administered are IL-1B inhibitors. These inhibitors of IL-1B which are the most commonly administered in chemotherapy are; C27H24FN30(RWJ67657) (Westra et al. 2004), NCX4040 (Ricciotti et al. 2010) and Celastrol (Li et al. 2016). On the other hand, the food/plant bioactive compounds with their IL-1B inhibitory effects are; apigenin ($1x10^{-6}$-$1x10^{-4}$ M/72h, in the embryonic mouse heart cell line, H9c2) (Gutierrez-Venegas et al. 2017), EGCG (50 μM/18h, in intervertebral disc cells) (Krupkova et al. 2014), quercetin (100 μM/24h, in orbital fibroblasts) (Yoon et al. 2011), resveratrol (100 μM724h, in human chondrocytes) (Limagne et al. 2016), L-arginine (0.4 mM/6h, in the colon cancer cell line, Caco-2) (Meng et al. 2017), lycopene (4 μM/48h, in peripheral blood mononuclear cells (Bessler et al. 2008), amygdalin (10 mg/Kg/d for 4 week supplementation), ascorbic acid (15 g intravenous administration within 1 d intervals for 1 week) (Mikirova et al. 2016), sulforaphane (40 μM/72h, in the gastric cancer cell lines; MGC803 and BGC823) (Wang et al. 2016), genistein (50 μmol/mL724, in the human

leukemic mast cell line, HMC-1) (Kim et al. 2014) and B-carotene (20 μmol/L/12h, in the gastric epithelial cell line, AGS cells) (Kim et al. 2011). These food/plant bioactive compounds might lead to a better prognose during the administrations of the IL-1B blockers by creating a synergism for a much stronger inhibition of the pro-inflammatory cytokine. Also, the following foods, herbs and their essential substances; blueberry (the polyphenols, e.g. anthocyanins), coffee (cafeic acid), grape (flavonoids, hydroxycinnamic acids, polyhydrophenols), garlic (diallyl sulfide), red pepper, hot chilli pepper (capsaicin), ginger (sesquiterpene hydrocarbons), rosemary, apples, bilberries, cranberries, pears, peppermint, lavender, oregano, holy basil, thyme and prunes (ursolic acid), vegetables from *Brassicaceae* family (sulforaphane), *Ginkgo biloba* (flavonoid glycosides and terpene trilactones) (10 μg/24h, in the foam cells, U937) and milk thistle (silymarin) (100 μg/mL724h, in the pancreatic beta cell line, MIN6N8a) might enhance the anti-inflammatory effect of the mentioned IL-1B inhibitors and food/plant bioactive compounds, via the synergism to inhibit the cytokine (Lee et al. 2009; Tang et al. 2015, Grzanna et al. 2004, Huang et al. 2009; Shukitt-Hale et al. 2008; Jung et al. 2008; Panico et al. 2006; Lin et al. 2008; Jiao et al. 2007 and Kim et al. 2014). During the administrations of all these mentioned IL-1B inhibitors and intakes of the IL-1B inhibiting food/plant bioactive compounds, a diet rich in n-3 Omega PUFAs might be contraindicated since these fatty acids increase the secretion of the cytokine. One of the crucial points to consider should be the use of extra virgin olive oil instead of Omega 3 PUFAs, if the treatment is based on the inhibition of IL-1B. Because, olive oil contains vanillic, p-coumaric, syringic, homovanilic and cafeic acids, kaempferol, oleuropein glycoside and tyrosol which inhibit the inflammatory cytokine (Miles et al. 2005), as in contrast with Omega 3 PUFAs. Finally, there is still no study about the sole effects of tocopherol and kaempferol on IL-1B. Although there is no study about the sole effect of folate on IL-1B, like tocopherol and kaempferol, in any cancer cell line, it is well documented that the vitamin has a dual effect in cancer. Not only healthy cells, but also cancer cells use the vitamin for nucleotide synthesis that promotes cell growth rapidly while building the blocks for DNA synthesis in the S-phase of the cell cycle (Garcia-Bennett et

al. 2011). But, the same dual effect was shown to be exploited by cancer cells in the study of Subia et al. (2014). More important is that, the procedure which is described in the study might be a novel and promising approach in anticancer treatments in a very near future. The study binds folate into folate receptors in all cells and administers silk fibroin-folate nanoparticles (500 μg mL^{-1} silk fibroins) which are loaded with the anticancer drug, doxorubicin (10 μg mL^{-1}/6h) and conjugates it with 10 mg folate, in human breast adenocarcinoma cells, MDA-MB-231. The drawback of the study is that, they also transfer the drug into healthy cells which might be an important side-effect. But the risk may be prevented by using antibodies which are only specific to the antigens of the targeted cancer cells. Such nanoparticules which target folate receptors in both cancer and healthy cells may also be loaded to transfer either anticancer drug or anti-cancerogenic food/plant-bioactive compounds. An important critic which conflicts with findings that claim the anticancerogenic effect of n-3 omega PUFAs belongs to MacLean et al. (2006). In the review, a total of thirty-eight prospective cohorts were included. Interestingly, many of the cohorts in the review do not provide any evidence to suggest a significant association between n-3 omega PUFAs and cancer, while some of them define Omega PUFAs as pro-oxidant rather than antioxidant. On the other hand, the initial parameter to evaluate the anticancer status of the fatty acids (and also all other food/plant bioactive compounds) should be the 'type of the treatment'. A clear example as previously mentioned is 'ROS'. Although ROS often appear as one of the initial predisposed factors for various diseases and disorders, 'killing tumor cells by ROS', has often been a novel anticancer approach in anticancer treatments, as previously mentioned. Firstly, the fatty acids have selective cytotoxicity with their ROS production towards cancer cells while having no toxicity or very little toxicity on normal cells (D'Eliseo and Velotti 2016). In a confirming manner, the treatment of the human pancreatic cancer cell lines, MIA-PaCa-2 and Capan-2, with 100 mM EPA or DHA/3d, was informed to kill tumor cells with ROS production of the fatty acids and subsequently induces caspase depended apoptosis (Fukui et al. 2013). Therefore, the anticancer drugs which target cancer cells by producing ROS might benefit from Omega 3 rich nutrition/supplementation by creating a

synergism to induce ROS, IL-1B and caspase activity for a much stronger apoptosis by gathering cancer cells in the intima wall of the vessel by IL-1B and targeting them with ROS. DHA and EPA do not only induce apoptosis by increasing the production and activity levels of ROS, caspase, IL-1B, DNA fragmentation and loss of mitochondrial membrane potential due to their ROS production, but also they decrease the phosphorylation of pro-oncogenic Akt. The treatment of the adenocarcinomic human alveolar basal epithelial cell line, A459, with DHA (100 μM/24h) inhibits Akt like the following chemotherapic agents which inhibit Akt; XL-147 (Foster et al. 2015), XL-765 (Dai et al. 2013), LY- 29002 (Yang et al. 2017), ISC-4, ISC-4 and Cetuximab combination (Allen et al. 2013), GSK690693 (Levy et al. 2009), MK-2206 (Malkomes et al. 2016), SF-1126 (Singh et al. 2016), NVP-BEZ235 (Xie et al. 2017), 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. 2015), phosphatidylinositol (3-5) triphosphate (PIP3) (Chang et al. 2014), GDC-0041 (Burrows et al. 2011), 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), lpatasertib (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). The treatments which administer these Akt inhibitors, might benefit from n-3 Omega PUFAs and the other food/plant bioactive compounds which inhibit PI3K/Akt due to the synergism to inhibit Akt more. It is important to overemphasize that the inhibition of Akt is not formed alone, instead, it always progresses through the inhibitions of the other cancerogenic enzymes and proteins, namely; HIF-1alpha, PIP3, PI3K, ERK1/2 and VEGF. Therefore, the nutrition style which includes Akt inhibiting food/ plant bioactive sources and Omega 3 PUFAs might also be a much more effective measure for the inhibitions of the Akt and the other Akt-related anticancerogenic proteins and enzymes. When the effect of the fatty

acids on the cancerogenic signaling, Hedgehog, the only study which is belong to Kharebava et al. (2015), observed an inhibitory effect of synaptamide, N-docosahexaenoylethanolamine, an endogenous metabolite of DHA (1 nM/48 h, in SMI-312 cortical neurons). Therefore, the Hedgehog inhibitors and the food/plant bioactive compounds which inhibit the signaling might benefit from these fatty acids. Finally, the expression of p38, the mitogen activated protein kinase, is 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 might lose their anticancerogenic effects by creating an antagonism, if n-3 Omega PUFAs rich food nutrition or supplementation is followed during their administrations.

Geelen et al. (2007) →	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.
Sasazuki et al. (2011) →	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.
Pot et al. (2008) →	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.

Folsom and Demissie (2004) →	442.965 person, 4.653 death / 55-69 years of age / alcohol and 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.
Brasky et al. (2014) →	22.494 women, 263 endometrial cancer / 9 years of follow up / 50-76 years of age / 50-76 years of age / smoking and 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.
Key et al. (2012) →	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.
Fu et al. (2015) →	(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 in the review).
Kubo et al. (2009) →	(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).
Long et al. (2013) →	n-3 Omega PUFAs during parenteral nutrition reduced inflammation and improved immune function in 60 patients after esophageal cancer surgery.

Kim et al. (2010) →	943 control, 929 distal large bowel cancer / 40-79 years of age / 2002-2006 / smoking adjusted, alcohol not / the highest quartile of the n-3 Omega PUFAs intake (0.88, 0.63-1.22, 95% CI) versus the lowest (0.49, 0.34-0.71, 95% CI) decreased the risk of distal large bowel cancer whereas n-6 Omega PUFAs increased the risk.

Table 15. The cohorts as related to the effect of Omega 3 PUFAs on cancer

As it is clearly understood from the cohorts about the effect of n-3 Omega PUFAs on cancer, between 2007 and 2015, in the Table above, there is an important amount of scientific data which indicates to the beneficial and protective effects of n-3 omega PUFAs against inflammation and cancer. Although some algae species and dinoflagellates appear as potentially rich sources of n-3 omega PUFAs for the very near future, there is currently a very limited number of researches as related to the effects of their comsumption rates on cancer. On the other hand, many studies administer the mega doses which are claimed to have anti-cancerogenic effect but the risk of the mega doses such as 'internal bleeding' have often been claimed. On the other hand, 8-10 g (which are extremely high) doses of the eicosapentoenoic acid and docosahexaenoic acid for 2-5 days preoperatively, and then 2 g/d postoperatively were informed to have associated with lower risk of bleeding (Akintoye et al. 2018). Confirmingly, the review of Begtrup et al. (2017) which includes 52 publications of healthy subjects and patients reveals that fish oil exposure in both surgical and healthy patients do not increase bleeding either during or after surgery. No need to mention the concerns about the risk of internal bleeding especially in cancer patients, but these latest findings and claims support the need for reconsideration of the current recommendations to stop fish oil or delay of surgical procedures in anti-cancer treatments. The effect mechanism of n-3 omega PUFAs on catecholamine metabolism, the daily recommended intakes for the patients who are suffered from both cancer, heart disease (particularly ventricular tachycardia and ventricular fibrillation) and/or diabet and

the risks of the supplementation of these fatty acids in pregnant women with cancer are the initial questions which are waiting to be studied and answered. More studies are needed to define the status of n-3 omega PUFAs in cancer. These studies should be double blind, placebo controlled, large big scale, randomised and cohort prospective studies rather than case control in small scale. But in a nutshell, the findings of all cohorts and meta-analysis which were published between 2004 and 2015 clearly indicate the necessity of fat preference in anti-cancer diets to be n-3 Omega fatty acids and olive oil. Additionally, lauric acid from coconut oil (100 μM/48h, on the breast cancer cell line, MCF-10 A) was determined to hamper tumor growth by inducing ROS, p21, c-Jun, c-fos, EGFR and ERK (Lappano et al. 2017). Hence, lauric acid and coconut oil might be beneficial and synergistic with the chemotherapeutics which induce ROS, p21, c-Jun, c-fos, EGFR and ERK, particularly, in colon, breast and endometrial cancer treatments. In contrast, red meat and dairy products should be avoided due to their higher Omega 6 and saturated fat contents since they increase the risk of cancer.

Arginine & glutamine rich nutrition	CD8 +T cell proliferation
Arginine &glutamine limitation	mTOR, Her2, PI3K, NF-kB inhibitors
≥400 μM arginine	COX2 inhibitors
Resveratrol, ascorbic acid, B6 limitation	HO-1 inhibitors
≥500 μM arginine	IL-8, IL-6/STAT3/TNF-α inhibitors
EGCG limitation	Akt, IL-6/STAT3 inhibitors
Increased genistein rich Ford intake	Increase in THA anticancerogenic effect of sorafenib
Genistein, lycopene, lutein, antheraxanthin, rhodamine	MDR1 inhibitors
Egg-derived peptides	Nrf2 inducers
Akt/PI3K/NF-kB/TNF-α/mTOR/ Her2 inhibiting BAC*	Foxo 1/3 inducing BAC*
Quercetin, lycopene, silibinin, sulforaphane, curcumin	AP-1 inhibitors/p27 inducers
Tangeretin, beta carotene, a fat rich diet	AP-1 inhibitors/p27 inducers

Sugar and fat May be included !	ROS and p38 inducing ana Nox inhibiting CHT*
NO/arginine/glutamine limitation	MMR inhibitors
Sesquiterpene rich nutrition	MDR1/P-gp/ABC inhibitors
Oleoresin, L-arginine, kakkonto, lycopene limitation	CD4 +T cell inhibitors
Omega 3 and probiotic rich nutrition	COX-2/NF-kB/VEGF inhibitors
Omega 3 rich but resveratrol, arginine, quercetin poor	AP-1 inhibitors
I3C, vitamin D, Omega 3 rich Ford limitation	IL-1β inhibitors
Coconut (lauric acid) oil	ROS inducing CTH
BAC*: Bioactive Compound	CTH*: Chemotherapy

Table 16. Some of the important recommended food/plant bioactive compounds for the specific chemotherapy

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THE STAGE IN WHICH WE HAVE ARRIVED PRESENTLY IN CANCER NUTRITION WITH ITS IMPORTANT REMARKS, QUESTIONS, DRAWBACKS AND PROMISES

Under the highlight of the findings belong to more than 1600 references in the review above, a huge number of critical points and conclusions to create a nutrition for cancer patients under chemotherapy may be ordered. As the items below clearly reveal, there can not be a standard and cliché nutrition like 'eating fish meat', 'plenty of vegetable and/ or fruit consumption', 'sufficient intake of fiber', or 'limitation of red meat and its products with milk and dairy products and processed foods'. These recommendations might only be useful for the healthy individuals, but not for the ones with cancer since the type of the chemotherapeutic agent and also food would have different effects on the cancerogenic pathways, proteins, enzymes and signals. Hence, the foods can only be selected and included into diet by considering and determining their synergistic or antagonistic effects on the chemotherapeutic agent. Otherwise, even the foods which are known as healthy might be contraindicated and alter the effect of the agent on the cancerogenic pathway, protein, enzyme or signal. Ironically, a food which is often introduced as harmful might be synergistic and enhance the anticancerogenic potential of the agent on these proteins, enzymes, pathways or signals. There can never be a cliche and standard nutrition for cancer patient. This aproach could never work and might even be contraindicated. The nutrition in cancer can only be designed as specific

to the chemotherapeutic agent and its effect mechanisms because of the synergistic or antagonistic interactions between the chemotherapeutic agent and bioactive compound, like the ones which are figured in Table 16 above. The final stage in which we have arrived with the present findings clearly indicates to the necessity of a hard work to design a nutrition which is specific to chemotherapy for the patient with cancer. Such approach should consider all the antagonisms, synergisms between food and drug (chemotherapeutic agent) and the effects of both drug and food/plant bioactive compound on the cancerogenic pathways, enzymes, proteins and signals. Only after the detailed evaluation of them which are listed one by one below, then a nutrition for the patient under chemotherapy could be designed. These items with their remarks, questions, drawbacks and promises are as follows;

1. Many fructose rich foods like onion, Brussels sprout, cabbage and spinach should not be blaimed to increase the risk of cancer because of their rich fructose contents while they are also rich sources of catalase and/or glutathione, fiber and many bioactive compounds with their anticancerogenic effects.
2. Folate, B_6 and tocopherol should be limited or avoided during the administrations of the agents which kill cancer cells by inducing ROS production.
3. Alcoholic beverages are contraindicated with the chemotherapeutic agents which inhibit Hedgehog signaling. On the other hand, resveratrol, genistein, curcumin, EGCG, vitamin D, baicalein, quercetin and apigenin and their rich sources might enhance the anticancerogenic effect of these drugs by creating a synergism via the inhibition of the signaling.
4. During the administrations of PI3K inhibitors, the limitation in cholesterol rich foods and the foods in high calorie should be essential since these inhibitors increase cholesterol.
5. Vitamin D supplementation or its rich food sources might be contraindicated with PI3K/Akt and VEGF inhibitors since it induces the expressions of PI3K, Akt and VEGF.

6. Although arginine and arginine rich foods are beneficial to boost the immune system, they might be contraindicated with the VEGF inhibitors.
7. Quercetin and its rich sources should be avoided or limited during the administrations of VEGFR and HIF-1α since the bioactive compound induce the expression of both VEGFR and HIF-1α.
8. Omega 3 and even Omega 6 fatty acids might be useful during the treatments with the MMP inhibitors since these faty acids inhibit the activity of MMP, while apigenin and apigenin rich nutrition might protect from the risk of cancer due to UV radiation by inhibiting the activity and expression of MMP.
9. Arginine deprivation does not necessarily induce apoptosis since cancer cells produce energy from glutamine via glutamine anaplerosis, while the deprivation of either arginine or glutamine is not promising and reasonable. Because both amino acids are esential for immune system. Furthermore, in case of arginin deprivation, it can be synthesized from glutamine.
10. Arginine and/or glutamine should better be restricted during the administrations of mTOR, PI3K and HO-1 inhibitors since the amino acids induce them.
11. Although ≥400 μM concentrations inhibit IL-6, -8, -10, HO-1, TNF-α and COX-2, reaching these concentrations in tumor microenvironment might not be possible.
12. FOXO inducing and Akt/PI3K/TNF-α/EGFR inhibiting food/plant bioactive compound rich nutrition might help to a better prognose, creating a synergism to increase the level of apoptosis.
13. Genistein, EGCG, lycopene and folic acid rich foods might be contraindicated during the treatments with Bcl-2 inhibitors and/or Bax/PUMA activators, because they induce Bcl-2 while inhibiting the pro-apoptotic Bax/PUMA.
14. The food/plant bioactive compounds and drugs which inhibit NF-kB and/or COX-2, might enhance the anticancerogenic potential of the food/plant bioactive compounds and drugs which inhibit one or some of the cancerogenic proteins, signaling and

pathways; HIF-1α, MMP9, TNF-α, VEGF, c-Jun, IL-1B, AP-1, Her2+, PI3K/Akt, Notch, Wnt, IL-8 and IL-6/STAT-3.

15. Resveratrol and its rich sources should be limited or avoided during the treatments with IL-6/STAT3/IL-8 inhibiting drugs since the food bioactive compound induces the expression of IL-8.
16. Sulforaphane and sulforaphane rich nutrition might lead to a better prognosis during the treatments with TNF-α inhibitors and Nrf2 inducers since it induces Nrf2 while suppressing TNF-α. But, vitamin D and I3C and their rich sources should be avoided or limited during the treatments with TNF-α inhibitors since both of them induce the gene. On the other hand, sulforaphane and its rich nutrition should be avoided or limited during the administrations of HO-1 inhibitors since it induces the gene.
17. The relation between Nrf2, food and cancer is closely connected with Cul3 and Keap1. Accordingly, the type of nutrition should inevitably change during the treatments which activate Nrf2 and inhibit Cul3 and Keap1, or vice versa. First, egg and its products as the protein source should be prefferred during the treatments with drugs which inactivate Nrf2 and Keap1 interaction and induce Nrf2. Similarly, Omega 3 fatty acids might be preferred during such treatments since the fatty acids activate Nrf2 while inhibiting Keap1. The diet should include beta carotene, lutein, I3C, curcumin, silymarin, genistein and alpha cryptoxhantin during the administrations of Nrf2 inducers since these bioactive compounds activate the gene and might create a synergy. During the treatments with Nrf2 inhibitors, wagonin, luteolin, quassinoid, trigonelline, cryptotanshinone, retinoic acid and chrysin and their rich food/plant sources should be exist in the diet since these bioactive compounds inhibit the gene and might lead to a better prognosis by creating a synergism via the inhibition of the gene in such treatments. By inhibiting Nrf2, luteolin increases the sensitivity of cancer cells to oxiplatin, bleomycin, doxorubicin and quassinoid, while brusatol increases the sensitivity of cancer cells to cisplatin, carboplatin, 5-fluorouracil, etoposide and paclitaxel and

trigonelline alleviates the resistance of cancer cells to etoposide. EGCG with its inducing effect and apigenin because of its unknown interaction with the gene, should better be avoided during the treatments with Nrf2 inhibitors.

18. Capsaicin and/or piperine could help to overcome MDR1 resistance in cancer cells to doxorubicin.
19. The form and micro-environment of food/plant bioactive compound is crucial and determines the effect of the compound. The anti-cancerogenic effect of resveratrol increases with the increase in acidity while the 'form' of vitamin A determines its anticancerogenic effect. Confirmingly, only lycopene, lutein, antheraxanthin and rhodamine inhibit MDR1 while alfa and beta carotene have not such effect. Even the sub-type of cancer cell line which is studied in a case control or cohort about 'cancer and food' might be a differential determiner. For example, lycopene has inhibitory effect on the breast cancer cell line, MDA-MB-468i but the same bioactive compound has no effect on the other sub-types of the same cancer, MCF-7 and SK-BR-3.
20. It might be useful to limit the intake of vitamin D_3, sulforaphane and folic acid during the treatments with Notch inhibitors since they induce the signaling.
21. The Notch inhibiting food/plant bioactive compounds and their rich sources might enhance the anticancerogenic effect of the inhibitors of Notch, Wnt, Hedgehog, VEGF and IL-6/STAT3, since cancer stem cells use all of them for their embriyonic development and differentiation.
22. Folic acid and folic acid rich nutrition should be limited during the treatments which administer miRNA and Lin28 inhibitors since it inhibits Let-7 while inducing Lin28B.
23. Cliché diet recommendations particularly during the administrations of p27 and p21 should definitely be avoided since fat which is often presented as harmful induces these inhibitors of cell cycle.
24. One of the initial barriers to be able to design a specific and standard anti-cancer diet is to know the dual functions

of the proteins, signaling and pathways which might act both cancerogenic or anticancerogenic. The inhibition of a cancerogenic signaling, protein or pathway by the means of a food/plant bioactive compound or a drug substance might also harm the healthy cells and weaken the immune system. On the other hand, though the inhibition of an oncogenic gene acts as apoptotic, the over-activation of the same gene might also be apoptotic, like the gene, p38. Then, the type of the food/plant, like the type of the chemotherapeutic agent, would have to change. For this reason, a standard, cliché nutrition prior, during and after cancer treatments could never be promising and might even be contraindicated with chemotherapy. The creation of such diet can only be dependent on the type of the targeted signaling, enzyme, pathway or gene. No need to mention that such creation would have to be specific to the chemotherapeutic agent which is specific to the targeted signaling, enzyme, pathway or gene. Accordingly, a fatty ground meat or a creamy dessert or a hamburger, which is often blamed as harmful and 'bad' food in a healthy diet, might even be useful and beneficial in cancer treatments if the treatment administers ROS inducers or cell cycle inhibitors (e.g. p21 and p27). Similarly, a fermented acidic beverage as combined with orange or tomato might ironically be beneficial, since resveratrol's bioavailability increases as proportional to the increase in acidity.

25. Arginine and arginine rich foods should better be limited or avoided during the administrations of MMR blockers since the amino acid induces MMR proteins.
26. The conjugation of specific monoclonal antibody to a particular type of cancer cell as combined with amygdalin, rhodanese and beta-glucosidase might be promising and a novel approach with less systemic toxicity. But first new studies to show the activity levels of beta-glucosidase and rhodanase in different types of cancer cells are needed.
27. The anticancerogenic potential depends on so many factors. One of the most effective determiners of the potential is the difference in chemical structure of the food/plant bioactive

compound. For example, flavones (e.g. apigenin and luteolin) inhibit T cells while flavonoles (e.g. morin) or flavonones (e.g. hesperetin) do not.

28. One of the most significant reasons for the necessity to create a specific anti-cancer diet which is specific to the chemotherapeutic agent is the different effects of lycopene, oleoresin, L-arginine, naringenin and sitostanol during the treatments with the CD+T cell inhibitors while these food/plant bioactive compounds are synergistic with these inhibitors. But, the food/plant compounds which inhibit Hedgehog signaling are antagonistic with the food/plant bioactive compounds, their sources and chemotherapeutic agents which inhibit CD+T cell proliferation, while ROS and CD+T cell inducing food/plant bioactive compounds are im synergism with Hedgehog inhibiting food/plant bioactive compounds and therapeutic agents.
29. Ironically, Omega 3 PUFAs might not be useful during the progress of cancer since the fatty acids might gain cancer cells the ability of homeostasis and defence to T helper and CDT cells by increasing the ratio of Treg cells and Foxp3 induction. Therefore it might be reasonable to avoid or limit the intake of these fatty acids during the treatments with the chemotherapeutic agents and food/plant bioactive compounds which inhibit CD4+T cells.
30. The present status of immunotherapy in cancer prevention and treatment does not seem promising because of its drawbacks like the severe harmful side effects, the suppression of antitumor immunity by the patient's own live regulatory T cells, the poor response of tumour cells with lower concentrations of PD-L1 and PD/PD-L1 and the absence of any response to PD-L1 inhibitors in tumour cells without CD80 protein. On the other hand, resveratrol, apigenin, L-arginine, curcumin and EGCG are in synergism with PD/PD-L1 blockers.
31. B_6 deficiency should be avoided particularly in the treatments with GRP78 inhibitors since the vitamin induces the chaperon. EGCG synergistically promotes taxol-and vinblastin-induced apoptosis. Besides, EGCG, resveratrol, α-tocopherol succinate,

kaempferol, ascorbic acid, luteolin, apigenin and lycopene inhibit the chaperons, GRP78 and Herp, and they might be useful to enhance the anticancerogenic potential of GRP78 and Herp inhibiting chemotherapeutics. On the other hand, sulforaphane and genistein should be avoided during the administrations of GRP78 and Herp inhibitors since they induce the expressions of both of them.

32. Kaempferol, quercetin, I3C, apigenin, genistein, biochanin-A, resveratrol, beta carotene, lycopene, calcitriol and folic acid might impose the anticancerogenic effect of the CDK inhibitors, p21 and p27, by creating a synergism via the inhibition of the enzymes.
33. The combined administrations of AP-1 (the inducer of growth signals) inhibitors and p27 inhibitors as a novel approach may take support from the intakes of quercetin, silibinin, lycopene, sulforaphane, curcumin, tangeterin, beta carotene and their rich sources. Fat limitation or elimination which is often recomended by cliche diets, should be avoided during the AP-1 inducers and p27 inhibitors since fat induces AP-1 while inhibiting p27.
34. Apigenin, folic acid, vitamin E succinate, EGCG, ascorbic acid, quercetin and sulforaphane, may enhance the anticancerogenic potential of the CDK, p38 and the chemotherapeutics which induce p38. On the other hand, lycopene, kaempferol, arginine and glutamine might synergistically increase the apoptotic effect of p38 inhibiting chemotherapeutics by suppressing the expression of the enzyme.
35. Ironically, the activation of (NADPH) oxidase as the main source of ROS and a poor diet from antioxidants may even stimulate phagocytosis of tumor cells. ROS, which might be one of the main reasons of various diseases and disorders, might activate both of the pro-apoptotic enzymes, PI3K and p38 MAPKs. But, decaffeinated green tea extract, folate, sulforaphane and quercetin, might be contraindicated with the treatments using Nox activators since they inhibit these enzymes. Similarly, ROS inducing foods and chemotherapeutic agents are in synergism with the MMR inhibitors. Kaempferol, EGCG, lycopene,

ascorbic acid, α-tocopherol, resveratrol and quercetin inhibit MMR proteins and might improve apoptotic effect of the MMR inhibitors.

36. The cancerogenic proteins, S1P, ABCC1, MRP1 and P-gp induce each other. The food/plant bioactive compounds, icaritine, biochanin A, silymarin, genistein, kaempferol, quercetin, apigenin, procyanidin, myricetin, wagonin, resveratrol, coumarin, sesquiterpenes inhibit the cancerogenic proteins and pathways, P-gp, ABC, MDR-1 and YB-1.
37. Curcumin inhibit cold shock proteins and may exhibit a synergism with cold shock protein inhibiting chemotherapeutics.,
38. One of the greatest barriers in cancer treatment is IL-22, which is produced by cancer cells by using the memory of the immune cells, CD4 +T, and which induces the secretion of another cytokine, IL-1B, to promote tumor growth.
39. Particulary, in the progress of cancer, DHA, EPA and safflower oil should be avoided since they decrease Th17 cells and increase Treg cells and Foxp3 while alleviating inflammation. The important note is that, GRP78 inhibiting food/plant bioactive compounds and chemotherapeutic agents suppress CD4 +T cell proliferation. On the other hand, COX-2 inhibition may block the CD+ T cell suppression. So, if the approach targets the administration of CD4 +T cell inhibitors, then the food/plant bioactive compounds which inhibit COX-2 should be avoided or limited.
40. Being insulin independent and GLUT5 cannot make fructose as the only and the biggest culprit in cancer progress since fructose activates ketohexokinase which rapidly metabolites fructose and depletes ATP. So, could it still be a literally scientific claim that fructose has a significant cancer inducing metabolism though ATP in cancer cells is depleted by a high fructose metabolism?. Besides, glucose is converted to fructose via the polyol pathway whereas glucose is metabolided to sorbitol and fructose. Therefore, the limitation of some of the fructose rich foods, e.g. corn-syrup, fruits and vegetables, would be meanless while the precursor of fructose is glucose which abundantly

exist in almost all foods. Additionally, most of the fructose rich foods like fruits and vegetables are also rich in many important anticancerogenic food bioactive compounds, like quercetin, I3C and resveratrol. Finally, both glucose and fructose overexpress and activate the proton exchangers and transporters which trigger the formation of tumour microenvironment as a result of hypoxia and increase in acidity (Warburg effect). Would it be correct to ignore glucose, but blame only fructose in the risk of cancer, while the proton exchangers and transporters which form tumor micro-environment are inhibited by some of the food bioactive compounds (e.g. resveratrol, EGCG, beta carotene, vanillin, catechol...) which are exist in planty amounts in particularly fructose rich fruits and vegetables.?

41. First, *Bacillus coagulans* and then *L. plantarum, B.infantis, S. thermophilus* and *L. rhamnosus*, orderly, are the most effective probiotics to induce CD4+/Foxp3/Tregs pathway while suppressing Th17 proinflammatory response. But, if the approach in the anticancer treatment is the elimination of 'data copying and transfer of cancer cells from CD4 +T cells and Foxp3, then these probiotics and their rich food sources like fermented meat and dairy products might be contraindicated with the CD4 +T and Foxp3 inhibitors.
42. Oral supplementation of *Bacillus rhamnosus* GG might be beneficial to avoid injury on lamina propria of intestinal epithelium which might be caused by COX-2 induction due to radiation. The probiotics, *Saccharomyces boulardii, Lactobacillus lactis, Lactobacillus casei* and *Lactobacillus reuteri* inhibit the pro-inflammatory and carcinogenic cytokines, PGE-2, IL-8, IL-1β, IL-6, TNF-α and IL-10, while *Saccharomyces boulardii* inhibits VEGFR. *Lactobacillus paracasei* BL23 may be useful in cancer patients by suppressing inflammation in IL-22 origin.
43. Opposite Omega-6 PUFAs, Omega-3 PUFAs; DHA and EPA has significant anticancerogenic effects on various cancers.
44. Omega-3 PUFAs may enhance the anticancerogenic potential of AP-1 inhibitors.

45. Like Omega-3 PUFAs, sulforaphane, beta carotene, alpha tocopherol, lycopene, genistein, vitamin D3, apigenin, ascorbic acid and EGCG are the bioactive compounds which have inhibitory effects on AP-1. Resveratrol and quercetin induce AP-1 and might be contraindicated with the AP-1 inhibitors.
46. Omega-3 PUFAs and resveratrol might have anticancerogenic benefit by activating Syndecan-1 and inhibiting MAPK/ERK. Thus, both of them may enhance Syndecan inducers and MAPK/ERK inhibitors.
47. Bax/Bim inducing and Bcl-2 inhibiting drug administrations could benefit from Omega -3 PUFAs.
48. Ascorbic acid, epigenin, vitamin D_3, resveratrol, quercetin, EGCG, curcumin, kaempferol, sıulforaphane, *Gonoderma lucidum*, arginine, genistein and Omega-3 PUFAs could create a much stronger inhibition of Wnt/β-catewnin signaling via their synergism with Wnt/β-catenin inhibitors.
49. COX-2 and NF-kB inhibitors might benefit from I3C, apigenin, kaempferol, quercetin, sulforaphane, beta carotene, lycopene, genistein, EGCG, amygdalin, alpha tocopherol, Omega-3 PUFAs and ascorbic acid to exhibit more anticancerogenic effect via their synergism to inhibit COX-2 and NF-kB.
50. The findings of all cohorts and meta-analysis between 2004 and 2015 clearly indicate the necessity of fat preference in anti-cancer diets to be olive oil and Omega-3 PUFAs. In contrast, the fat intakes from red meat and dairy product should be avoided or limited.

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THE FINAL CONCLUSION

All the findings of 1650 reference which are consisted of cohorts, case control studies and theories in the review clearly indicate to significant anticancerogenic but also cancerogenic effects, depending on their association, and interaction with the signaling, pathways and/or enzymes. Therefore, an anticancer diet could only be designed after the determinations of the interactions of each food on each pathway, signaling and/or enzyme. For example, the list of the food/plant bioactive compounds and their rich sources which have inhibitory effect on VEGF and which might be complementary to the VEGF inhibiting chemotherapy is different from the list of the food/plant bioactive compounds which might enhance the anticancerogenic potential of the chemotherapy which target cancer cells by producing ROS. On the other hand, the food/plant bioactive compounds and their rich sources which inhibit Hg, PI3K/Akt/mTOR, TNF-α, COX-2/NF-kB, IL-6/STAT3/IL-8, Wnt/β-catenin and VEGF, and the food/plant bioactive compounds and their rich sources which induce ROS and Bax, are synergistic with each other. Their combination in the diet might yield a much stronger anticancerogenic effect via the creation of a synergism to target cancer cells by producing ROS and Bax while inhibiting Hg, PI3K/Akt/mTOR, TNF-α, COX-2/NF-kB, IL-6/STAT3/IL-8, Wnt/β-catenin and VEGF. Each chemotherapeutic agent or each group of chemotherapeutics which are classified according to their inhibiting or inducing effect on the pathway, signaling and enzyme requires a unique, complementary food/plant bioactive compound or its rich source with the same effect. Only

after the determination and a detailed analysis of the synergistic and antagonistic food/plant bioactive compounds and chemotherapeutic agents, then only the food/plant bioactive compounds which have synergism with the chemotherapeutic agent or agents should have been included into the diet. In a nutshell, the meaning of the anticancer food and diet is 'being specific to the prescribed chemotherapeutic agent with the same effect mechanisms'.

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REFERENCES

1. Abdalah, R., Wei, L., Francis, K. and Yu, S. P. 2006. Volinomycin-induced apoptosis in Chinese hamster ovary cells. Neuroscience Letters. 405(1-2): 68-73
2. Abdallah, E. S. H. and Badary, D. M. 2017. Folic acid protects against lead acetate-induced hepatotoxicity by decreasing NF-kB, IL-1β production and lipid peroxidation mediated cell injury. Pathophysiology. 24(1): 39-44, https://doi.org/10.1016/j.pathoplys.2017.02.002
3. Abdel Malek, M. A., Jagannathan, S., Malek, E., Sayed, D. M., Elgammal, S. A., Abd El-Azeem, H. G., Thabet, N. M. and Driscoll, J. J. 2015. Molecular chaperone GRP78 enhances aggresome delivery to autophagosomes to promote drug resistance in multiple myeloma. Oncotarget. 6(5): 3098-110
4. Abdullah, A. and Ravanan, P. 2018. Kaempferol mitigates endoplasmic reticulum stress induced cell death by targeting caspase 3/7. Scientific Reports. 8: 2189, doi: 10.1038/s41598-018-20499-7, 15 pages
5. Abe, H., Ishikawa, W., Kushima, T., Nishimura, T., Mori, C., Onuki, A., Suzuki, T., Ishii, Y., Kansaku, N., Miyazaki, Y., Tanaka, K., Morita, H. and Takizawa, T. 2013. Nitric oxide induces vascular endothelial growth factor expression in the rat placenta in vivo and in vitro. Biosci. Biotechnical. Biochem. 77(5): 971-976

6. Abravanel, D. L., Belka, K. G., Pan, T., Pant, D. K., Collins, M. A., Sterner, C. J. and Chodosh, L. A. 2015. Notch promotes recurrence of dormant tumor cells following HER2/nem-targeted therapy. J Clin Invest. 125(6): 2484-2496
7. Adebamowo, C. A., Cho, E., Sampson, L., Katan, M. B., Spiegelman, D., Willett, W. C. and Holmes, M. D. 2005. Dietary flavonols and flavonol-rich foods intake and the risk of breast cancer. International Journal of Cancer. 114(4): 628-633
8. Adikesavan, G., Vinayagam, M. M., Abdulrahman, L. A. and Chinnasamy, T. 2013. (-)-Epigallocatechin-gallate (EGCG) stabilize the mitochondrial enzymes and inhibits the apoptosis in cigarette smoke-induced myocardial dysfunction in rats. Molecular Biology Reports. 40(12): 6533-6545
9. Aggarwal, B. B., Bhardwaj, A., Aggarwal, R. S., Seeram, N. P., Shishodia, S. and Takada, Y. 2004. Role of resveratrol in prevention and therapy of cancer: Preclinical and clinical studies. Anticancer Research. 24(5A): 2783-2840
10. Ahmad, R., Rasheed, Z. and Ali, R. 2009. Hydroxyl radical damaged thymidine-5-monophosphate presents unique apitopes for cancer antibodies. The Open Cancer Immunology Journal. 2(1): 10-17, doi: 10.2174/1876401000902010010
11. Ahmed, N. and Furth, A. J. 1992. Failure of common glycation assays to detect glycation by fructose. Clin Chem. 38(7): 1301-3
12. Ahmed, S., Mundhe, N., Borgohain, M., Chowdhury, L., Kwatra, M. and Bolshette, N. 2016. Diosmin modulates the NF-kB signal transduction pathways and downregulation of various oxidative stress markers in Alloxan-induced diabetic nephropathy. Inflammation. 39(5): 1783-1797
13. Ahn, H. J., Kim, K. I., Hoan, N. N., Kim, C. H., Moon, E., Choi, K. S., Yang, S. S. and Lee, J. 2014. Targeting cancer cells with reactive oxygen and nitrogen species generated by atmopheric pressure air plasma. Plos One. 9(1): e86173, 12 pages, doi: 10. 1371/ journal. pone. 0086173
14. Akintoye, E., Sethi, P., Harris, W. S., Thompson, P. A., Marchioli, R., Tavazzi, L., Latini, R., Pretorius, M., Brown, N. J., Libby, P. and Mozaffarian, D. 2018. Fish oil and perioperative bleeding.

Circ Cardiovasc Qual Outcomes. 11(11): e004584, doi: 10.1161/CIRCOUTCOMES.118.004584

15. Ala-aho, R. and Kahari, V. M. 2005. Collagenase in cancer. Biochimie. 87(3-4): 273-86
16. Alaoui-Jamali, M.A., Bismar, T.A., Gupta, A., Szarek, W.A., Su, J., Song, W., Xu, Y., Xu B., Liu, G., Vlahakis, J.Z., Roman, G., Jiao, J. and Schipper, H. M. 2009. A novel experimental heme oxygenase-1-targeted therapy for hormone-refractory prostate cancer. Cancer Res. 69(20):8017-24
17. Alarmo, E. L., Parssinen, J., Ketolainen, J. M., Savinainen, K., Karhu, R. and Kallioniemi, A. 2009. BMP7 influences proliferation, migration, and invasion of breast cancer cells. Cancer Lett. 275(1):35-43, doi: 10.1016/j.canlet.2008.09.028
18. Alcaraz, M. J., Fernandez, P. and Guillen, M. I. 2003. Anti-inflammatory actions of the heme oxygenase-1 pathway. Curr Pharm Des. 9(30): 2541-51
19. Alexandrou, C., Al-Aqbi, S. S., Higgins, J. A., Boyle, W., Karmokar, A., Andreadi, C., Luo, J., Moore, D. A., Viskaduraki, M., Blades, M., Murray, G. I., Howells, L. M., Thomas, A., Brown, K., Cheng, P. N. and Rufini, A. 2018. Sensitivity of colorectal cancer to arginine deprivation therapy is shaped by differential expression of urea cycle enzymes. Scientific Reports. 8: 12096, doi: 10.1038/s41598-018-30591-7
20. Al-Hendy, A., Diamond, M. P., Boyer, T. G. and Halder, S. K. 2016. Vitamin D_3 inhibits Wnt/β-catenin and mTOR signaling pathways in human uterine fibroid cells. The Journal of Clinical Endocrinology & Metabolism. 101(4): 1542-1551
21. Aljada, A., Ghanim, H., Mohanty, P., Hofmeyer, D., Tripathy, D. and Dondona, P. 2001. Hydrocortisone suppresses intranuclear activator-protein-1 (AP-1) binding activity in mononuclear cells and plasma matrix metalloproteinase 2 and 9(MMP-2 and MMP-9). J Clin Endocrinol Metab. 86(12): 5988-91
22. Allen, J. E., Gallant, J. N., Dicker, D. T., Amin, S., Irby, B. B., Sharma, A. K. and El-Deiry, W. S. 2013. The Akt inhibitor ISC-4 synergizes with cetuximab in 5-FU-resistant colon cancer. PlosOne. 8(3): e59380, doi:10.1371/journal.pone.0059380, 8 pages

23. Allen, L. F., Lenehan, P. F., Eiseman, I. A., Elliott, W. L. and Fry, D. W. 2002. Potential benefits of the irreversible pan-erbB inhibitor, canertinib (CI-1033) in the treatment of breast cancer. Semin Oncol. 29(3): 11-21
24. Allen, M. J., Fan, Y., Monk, J. M., Hou, T. Y., Barhoumi, R., McMurray, D. N. and Chapkin, R. S. 2014. N-3 PUFAs reduce T-helper 17 cell differentiation by decreasing responsiveness to interleukin-6 in isolated mouse splenic $CD4^+$ T cells. J Nutr. 144(8): 1306-1313
25. Allfrey, V. G., Boffa, L. C. and Vidali, G. 1977. Selective inhibition with sodium cyanate of protein synthesis in colon cancer cells. Cancer. 40(5 suppl): 2692-8
26. Alumkal, J. J., Slottke, R., Schwartzman, J., Cherala, G., Munar, M., Graff, J. N., Beer, T. M., Ryan, C. W., Koop, D. R., Gibbs, A., Gao, L., Flamiatos, J. F., Tucker, E., Kleinschmidt, R. and Mori, M. 2015. A phase II study of sulforaphane-rich broccoli sprout extracts in men with recurrent prostate cancer. Invest New Drugs. 33(2): 480-9
27. Ambati, R. R., Moi, P. S., Ravi, S. and Aswathanarayana, R. G. 2014. Astaxanthin: sources, extraction, stability, biological activities and its commercial applications-A review. Mar Drugs. 12(1): 128-152, doi: 10.3390/md12010128
28. Ambroz, M., Matouskova, P., Skarka, A., Zajdlova, M., Zakova, K. and Skalova, L. 2017. The effects of selected sesquiterpenes from *Myrica rubra* essential oil on the efficacy of doxorubicin in sensitive and resistant cancer cell lines. Molecules. 22(6): 1021, doi: 10.3390/molecules22061021, 10 pages
29. Ames, B. N. 2001. DNA damage from micronutrient deficiencies is likely to be a major cause of cancer. Mutation Research. 475(1-2): 7-20
30. Amoroso, F., Falzoni, S., Adinolfi, E., Ferrai, D. and Virgilio, Di, F. 2012. The P2X7 receptor is a key modulator of aerobic glycolysis. Cell Death Dis. 3(8):e370, doi: 10.1038/cddis.2012.105, 18 pages
31. Ancrile, B., Lim, K. H. and Counter, C. M. 2007. Oncogenic Ras-induced secretion of IL-6 is required for tumorigenesis. Genes Dev. 21(14): 1714-9

32. Andersen, P., Uosaki, H., Shenje, L. and Kwon, C. 2012. Non-canonical Notch signaling: Emerging role and mechanism. Trends Cell Biol. 22(5): 257-265
33. Andreeva, O. A., Ivashev, M. N., Ozimina, I. I. and Maslikova, G. V. 1998. Diosmetin glycosides from Caucasian vetch: Isolation and study of biological activity. Pharmaceutical Chemistry Journal. 32(11): 595-597
34. Anglesio, M. S., George, J., Kulbe, H., Friedlander, M., Rischin, D., Lemech, C., Power, J., Coward, J., Cowin, P. A., House, C. M., Chakravarty, P., Gorringe, K. L., Campbell, I. G., Australian Ovarian Cancer Study Group, Okamoto, A., Birrer, M. J., Huntsman, D. G., de Fazio, A., Kalloger, S. E., Balkwill, F., Gilks, C. B. and Bowtell, D. D. 2011. IL6-STAT3-HIF signaling and therapeutic response to the angiogenesis inhibitor sunitinib in ovarian clear cell cancer. Clin Cancer Res. 17(8): 2538-48
35. Antonioli, L., Pacher, P., Vizi, E. S. and Haskö, G. 2013. CD39 and CD73 in immunity and inflammation. Trends Mol Med. 19(6): 355-367
36. Antonsson, B., Montessuit, S., Sanchez, B. and Martinou, J. 2001. Bax is present as a high molecular weight oligomer/ complex in the mitochondrial membrane of apoptotic cells. J Biol Chem. 276(15): 11615-23
37. Antoon, W. J., Bratton, R. M., Guillot, M. L., Wadsworth, S., Salvo, A.V. and Burow, E. M. 2012. Inhibition off p38-MAPK alters SRC coactivation and estrogen receptor phosphorylation. Cancer Biol Ther. 13(11): 1026-1033
38. Ara, T. and Declerck, Y. A. 2010. Interleukin-6 in bone metastasis and cancer progression. Eur J Cancer. 46(7): 1223-31
39. Arafa, H. F. 2009. Possible contriution of beta-glucosidase and caspases in the cytotoxicity of glufosfamide in colon cancer cells. European Journal of Pharmacology. 616(1-3): 58-63
40. Arai, Y., Watanabe, S., Kimira, M., Shimoi, K., Mochizuki, R. and Kinae, N. 2000. Dietary intakes of flavonols, flavones and isoflavones by Japanese women and the inverse correlation between quercetin intake and plasma LDL cholesterol concentration. J Nutr. 130(9): 2243-50

41. Arlt, A., Sebens, S., Krebs, S., Geismann, C., Grossmann, M., Kruse, M. L., Schreiber, S. and Schafer, H. 2013. Inhibition of the Nrf2 transcription factor by the alkaloid trigonelline of the Nrf2 transcription factor by the alkaloid trigonelline renders pancreatic cancer cells more susceptible to apoptosis through decreased proteasomal gene expression and proteasome activity. Oncogene. 32: 4825-4835, doi: 10.1038/onc.2012.493
42. Arnal, J. F., Münzel, T., Venema, R. C., James, N. L., Bai, C. L., Mitch, W. E. and Harrison, D. G. 1995. Interactions between L-arginine and L-glutamine change endothelial NO production. An effect independent of NO synthase substrate availability. J Clin Invest. 95(6): 2565-2572
43. Aronson, J. P. and Zhang, J. 2016. Palmar plantar pustulosis responding to high-dose folic acid plus vitamins B6 and B12. JADD Case Rep. 2(1): 19-21, doi: 10.1016/j.jdcr.2015.10.004
44. Arora, A. and Shukla, Y. 2003. Modulation of vinca-alkaloid induced P-glycoprotein expression by indole-3-carbinol. Cancer Letters. 189(2): 167-173
45. Asaduzzaman, M., Wang, Y. and Thorlacius, H. 2008. Critical role of p38 mitogen-activated protein kinase signaling in septic lung injury. Crit Care Med. 36(2): 482-8
46. Asgharzadeh, R. M., Barar, J., Pourseif, M. M., Eskandani, M., Niya, J. M., Mashayekhi, R. M. and Omidi, Y. 2017. Molecular machineries of pH dysregulation in tumor microenvironment: potential targets for cancer therapy. BioImpacts. 7(2): 115-133
47. Aster, J. C. and Blacklow, S. C. 2012. Targeting the Notch pathway: twists and turns on the road to rational therapeutics. J Clin Oncol. 30(19): 2418-20
48. Aster, J. C., Pear, W. S. and Blacklow, S. C. 2017. The varied roles of Notch in cancer. Annu Rev Pathol. 12: 245-275, doi: 10.1146/annurev-pathol-052016-100127
49. Atta, M. H., El-Rehani, A. M., Raheim, A. S. and Moneim Abdel, F. G. 2008. Lowering homocysteine decreases levels and expression of VEGF and endostatin. Journal of Surgical Research, 146:202-210, doi:10.1016/j.jss.2007.04.038

50. Attia, G. M., Elmansy, R. A. and Algaidi, S. A. 2017. Silymarin decreases the expression of VEGF-A, iNOS and caspase-3 and preserves the ultrastructure of cardiac cells in doxorubicin induced cardiotoxicity in rats: a possible protective role. Int J Clin Exp Med. 10(2): 4158-4173
51. Atwood, S. X., Chang, A. L. S. and Oro, A. E. 2012. Hedgehog pathway inhibition and the race against tumor evolution. J Cell Biol. 199(2) 193-197
52. Audo, I., Darjatmoko, S. R., Schlamp, L. C., Lokken, J. M., Lindstrom, J. M., Albert, M. D. and Nickells, R. W. 2003. Vitamin D analogues increase p53, p21, and apoptosis in xenograft model of human retinoblastoma. Investigative Ophthalmology & Visual Science. 44: 4192-4199, doi: 10.1167/İOVS.02-1198
53. Aune, D., Chan, D. S. M., Lau, R., Vieira, R., Greenwood, D. C., Kampman, E. and Norat, T. 2011. Dietary fibre, whole grains, and risk of colorectal cancer: systematic review and dose-response meta-analysis of prospective studies. BMJ. 343: d6617, doi: 10.1136/bmj.d6617, 20 pages
54. Auyeung, K. K., Han, Q. B. and Ko, J. K. 2016. *Astragalus membranaceus*: A review of its protection against inflammation and gastrointestinal cancers. Am J CLin Med. 44(1): 1-22, doi: 10.1142/S0192415X16500014
55. Avisetti, R. D., Babu, S. K. and Kalivendi, V. S. 2014. Activation of p38/JNK pathway is responsible for Embelin induced apoptosis in lung cancer cells: Transitional role of reactive oxygen species. PlosOne. 9:1 doi: 10.1371/journal.pone.0087050, 10 pages.
56. Azarenko, O., Okouneva, T., Singletary, K. W., Jordan, M. A. and Wilson, L. 2008. Suppression of microtubule dynamic instability and turnover in MCFT breast cancer cells by sulforaphane. Carcinogenesis. 29(12): 2360-8
57. Baardseth, P. and Slinde, E. 1983. Peroxidase, catalase and palmitoyl-CoA hydrolase activity in blanched carrot tubes after storage at -20 °C. 34(11):1257-1262
58. Bachegowda, L., Morrone, K., Winski, S. L., Mantzaris, I., Bartenstein, M., Ramachandra, N., Giricz, O., Sukrithan, V.,

Nwankwo, G., Shahnaz, S., Bhagat, T., Bhattacharyya, S., Assal, A., Shastri, A., Gordon-Mitchell, S., Pellagattis, A., Boultwood, J., Schinke, C., Yu, Y., Guha, C., Rizzi, J., Garcus, J., Brown, S., Wollenberg, L., Hogeland, G., Wright, D., Munson, M., Rodriguez, M., Gross, S., Chantry, D., Zou, Y., Platanias, L., Burgers, L. E., Pradhan, K., Steidl, U. and Verma, A. 2016. Pexmetinib: A novel dual inhibitor of TieZ and p38 MAPK with efficacy in preclinical models of myelodysplastic syndromes and acute myeloid leukemia. Cancer Res. 76(16): 4841-4849

59. Bai, F., Qi, N., Wu, C. and Nie, Y. 2013. A new insight into the effect of heme oxygenase-1 in progress of malignant tumors. Journal of Gastroenterology and Hepatology Research. 2(1): 353-358

60. Bai, H., Jin, H., Yang, F., Zhu, H. and Cai, J. 2014. Apigenin induced MCF-7 cell apoptosis-associated reactive oxygen species. Scanning. 36(6): 622-31

61. Bai, L., Weng, J., Chiu, C., Wu, C., Yeh, S., Sargeant, A. M., Lin, P. and Liao, Y. 2013. OSU-A9, an indole-3-carbinol derivative, induces cytotoxicity in acute myeloid leukemia through reactive oxygen species-mediated apoptosis. Biochemical Pharmacology. 86(10): 1430-1440

62. Bai, X., Cerimele, F., Ushio-Fukai, M., Wagas, M., Campbell, P. M., Govindarajan, B., Der, C. J., Battle, T., Frank, D. A., Ye, K., Murad, E., Dubiel, W., Soff, G. and Arbiser, J. L. 2003. Honokiol, small molecularweight natural product, inhibits angiogenesis in vitro and tumor growth in vivo. Journal of Biological Chemistry. 278(37): 35501-7

63. Bai, Y., Lu, H., Wu, C., Liang, Y., Wang, S., Lin, C., Chen, B. and Xia, P. 2014. Resveratrol inhibits epithelial-mesenchymal transition and renal fibrosis by antagonizing the hedgehog signaling pathway. Biochemical Pharmacology. 92(3): 484-493

64. Bailey, T. S., Miron, L. P., Choi, J. Y., Kochupurakkal, B., Maulik, G., Rodig, J. S., Tian, R., Foley, M. K., Bowman, T., Miron, A., Brown, M., Iglehart, J. D. and Debajit, B. K. 2014. Nuclear factor kappa B activation-induced anti-apoptosis renders HER2 positive cells drug resistant and accelerates tumor growth. Mol Cancer Res. 12(3): 408-420

65. Baker, A. T., Zlobin, A. and Osip, C. 2014. Notch-EGFR/HER2 bidirectional crosstalk in breast cancer. Front Oncol. 4:360, doi: 10.3389/fronc. 2014. 00360, 15 pages
66. Balaji, S. A., Udupa, N., Chamallamudi, M. R., Gupta, V. and Rangarajan, A. 2016. Role of the drug transporter ABCC3 in breast cancer chemoresistance. PlosOne. 11(5): e0155013, doi: 10.1371/journal.pone.0155013, 22 pages.
67. Balakrishnan, K., Peluso, M., Fu, M., Rosin, N. Y., Burger, J. A., Wierda, W. G., Keating, M. J., Faia, K., O'Brien, S., Kutok, J. L. and Gandhi, V. 2015. The phosphoinositide 3-kinase (PI3K)-delta and gamma inhibitor, IPI-145 (Duvelisib), overcomes signals from the PI3K/AKT/S6 pathway and promotes apoptosis in CLL. Leukemia. 29(9): 1811-22
68. Ballin, N. Z. and Sorensen, A. T. 2014. Coumarin content in cinnamon containing products on the Danish market. Food Control. 38: 198-203, http://dx.doi.org/10.16/j. foodcont.2013.10.014
69. Balzeau, J., Menezes, R. M., Cao, S. and Hagan, P. J. 2017. The LIN28/let-7 pathway in cancer. Front Genet. 8:31, doi: 10.3389/ fgene.2017.00031, 16 pages
70. Bandi, N. and Kompella, U. B. 2001. Budesonide reduces vascular endothelial growth factor secretion and expression in airway (Calu-1) and alveolar (A549) epithelial cells. Eur J Pharmacol. 425(2): 109-16
71. Bandukwala, H. S., Gagnon, J., Togher, S., Greenbaum, J. A., Lamperti, E. D., Parr, N. J., Molesworth, A. M. H., Smithess, N., Lee, K., Witherington, J., Tough, D. F., Prinjha, R. K., Peters, B. and Roo, A. 2012. Selective inhibition of CD4+ T-cell cytokine production and autoimmunity by BET protein and c-Myc inhibitors. PNAS. 109(36): 14532-14537
72. Banerjee, A., Baksi, K. and Banerjee, D. 2008. Tunicamycin inhibits VEGF-induced vessel sprouting in Matrigel. Cancer Research. 99th AACR Annula Meeting-Apr 12-16, 2008, San Diego, CA., USA.
73. Banerjee, P., Basu, A., Arbiser, J. L. and Pal, S. 2013. The natural product honokiol inhibits Calcineurin inhibitor-induced

and Ras-mediated tumor promoting pathways. Cancer Lett. 338(2): 292-299

74. Banerjee, P., Basu, A., Wegiel, B., Otterbein, L. E., Mizumura, K., Gasser, M., Waaga-Gasser, A. M., Choi, A. M. and Pal, S. 2012. Heme oxygenase-1 promotes survival of renal cancer cells through modulation of apoptosis and autophagy-regulating molecules. The Journal of Biological Chemistry. 287(38): 32113-32123

75. Bang, Y., Kang, Y., Alsina, M., Wainberg, Z. A., Chau, I., Zhu, J., Chan, W. Y., Patel, P. H., Meng, R. D. and Ajani, J. A. 2014. JAGUAR: A randomized phase II study of the Akt inhibitor ipatasertib (GDC-0068) versus placebo in combination with mFOLFOX6 chemotherapy in patients (pts) with locally advanced or metastatic HER2-negative gastric (G) or gastrooesophageal junction (GEJ) adenocarcinoma. (2014 ASCO Annual Meeting. Session Type and Session Title: General Poster Session, Gastrointestinal (noncolorectal) cancer. Abstract Number: TPS4147). J Clin Oncol. 32: 5s, 2014 (suppl, abstr TPS4147)

76. Bao, C., Ko, J., Park, H., Kim, M. C., Kim, J., Auh, J. and Lee, H. J. 2015. Sulforaphane inhibited tumor necrosis factor-α induced migration and invasion in estrogen receptor negative human breast cancer cells. Food Sci Biotechnol. 24(1): 347-351, doi: 10.1007/s10068-015-0046-7

77. Bao, Y., Ng, K., Wolpin, B. M., Michaud, D. S., Giovannucci, E. and Fuchs, C. S. 2010. Predicted vitamin D status and pancreatic cancer risk in two prospective cohort studies. British Journal of Cancer. 102(9): 1422-1427

78. Barber, M.D., Ross, J.A., Voss, A.C., Tisdale, M.J. and Fearon, K.C.H. 1999. The effect of an oral nutritional supplement enriched with fish oil on weight-loss in patients with pancreatic cancer. British Journal of Cancer. 81(1): 80–86, doi:10.1038/sj.bjc.6690654

79. Barberan, F. A. T., Gil, MI., Tomas, F., Ferreres, F. and Arques, A. 1985. Flavonoid aglycones and glycosides from *Teucrium gnaphalodes*. J Nat Prod. 48(5): 859-860

80. Barrera, P., Sülsen, V. P., Lozano, E., Rivera, M., Beer, F. M., Tonn, C., Martino, V. S. and Sosa, M. A. 2013. Natural sesquiterpene lactones induce oxidative stress in *Leishmania Mexicana*. Evidence-Based Complementary and Alternative Medicine. Volume 2013, Article ID163404, 6 pages, https://doi.org/10.1155/2013/163404

81. Barrett, J. S. and Glbson, P. R. 2007. Clinical ramifications of malabsorption of fructose and other short-chain carbohydrates. Practical Gastroenterology. 31(8): 51-65

82. Baruah, M. M., Khandwekar, A. P. and Sharma, N. 2016. Quercetin modulates Wnt signaling components in prostate cancer cell line by inhibiting cell viability, migration and metastases. Tumor Biology. 37(10): 14025-14034

83. Basu, D., Salgado, C. M., Bauer, B., Khakoo, Y., Patel., J. R., Hoehl, R. M., Bertolini, D. M., Zabec, J., Brzozowski, M. R. and Reyes-Mugica, M. 2018. The dual PI3K/mTOR inhibitor Omipalisib/GSK2126458 inhibits clonogenic growth in oncogenically-transformed cells from neurocutaneous melanocytosis. Cancer Genomics Proteomics. 15(4): 239-248

84. Beauvaris, M. D., Burbach, J. B. and Rapraeger, C. A. 2004. The syndecan-1 ectodomain regulates αbβ3 integrin activity in human mammary carcinoma cells. The Journal of Cell Biology. 167(1): 171-181, doi:10.1083/jcb.200404171

85. Begtrup, K. M., Krag, A. E. and Hvas, A. M. 2017. No impact of fish oil supplements on bleeding risk: a systematic review. Dan Med J. 64(5): pii. A5366

86. Belfiore, A. and Frasca, F. 2008. IGF and insulin receptor signaling in breast cancer. J Mammary Gland Biol Neoplasia. 13(4): 381-406

87. Bello, O. M., Nieva, L. O., Paredes, A. C., Gonzalez, A. M. F., Zavaleta, L. R. and Lizano, M. 2015. Regulation of the Wnt/β-Catenin Signaling Pathway by Human Papillomavirus E6 and E7 Oncoproteins. Viruses. 7(8): 4734–4755.

88. Bellosta, S., Baetta, R., Canavesi, M., Comporato, C., Granata, A., Monetti, M., Cairoli, F., Puglisi, L. and Corsini, A. 2007. Raloxifene inhibits matrix metalloproteinases expression and

activity in macrophages and smooth muscle cells. Pharmacol Res. 56(2): 160-7

89. Bendrik, C. and Dabrosin, C. 2009. Estradiol increases IL-8 secretion of normal human breast tissue and breast cancer in vivo. J Immunol. 128(1): 371-8, doi: https:// doi.org / 10.4049 / jimmunol.182.1.371

90. Berman, D. M., Karhadkar, S. S., Maitra, A., Montes De Oca, R., Gerstenblith, M. R., Briggs, K., Parker, A. R., Shimada, Y., Eshleman, J. R., Watkins, D. N. and Beachy, P. A. 2003. Widespread requirement for Hedgehog ligand stimulation in growth of digestive tract tumours Nature. 425(6960): 846-51

91. Berndt, S. I., Carter, H. B., Landis, P. K., Hallfrisch, J., Rohrman, S., Metter, J. and Platz, E. A. 2005. Prediagnostic plasma vitamin C levels and the sunsequent risk of prostate cancer. Nutrition. 21(6):686-90

92. Berneis, K., Bollag, W., Kofler, M. and Luthy, H. 1966. The enhancement of the after effect of ionizing radiation by a cytotoxic methyhydrazine derivative. Eur J Cancer. 2 (1): 43-49, PMID: 5962293

93. Bernfeld, E., Menon, D., Vaghela, V., Zerin, I., Faruque, P., Frias, M. A. and Foster, D. A. 2018. Phospholipase d-dependent mTORC1 activation by glutamine. JBC Papers in Press. Published on Semptember 7, 2018 as Manuscript RA118.004972, http:// www.jbc.org/cgi/doi/10.1074/ jbc.RA118.004972, 19 pages.

94. Bessler, H., Salman, H., Bergman, M., Alcalay, Y. Ana Djaldetti, M. 2008. In vitro effect of lycopene on cytokine production by human peripheral blood mononuclear cells. Immunol Invest. 37(3): 183-90

95. Betancur, P. A., Abraham, B. J., Yiu, Y. Y., Willingham, S. B., Khameneh, F., Zarnegar, M., Kuo, A. H., McKenna, K., Kojima, Y., Leeper, N. J., Ho, P., Gip, P., Swigut, T., Sherwood, R. I., Clarke, M. F., Somlo, G., Young, R. A. and Weissman, I. L. 2017. A CD47-associated super-enhancer links pro-inflammatory signaling to CD47 upregulation in breast cancer. Nat Commun. 8: 14802, doi: 10.1038ncomms14802, 14 pages

96. Bhatt, P. A., Bhende, M. P., Sin, S., Roy, D., Dittmer, P. D. and Damania, B. 2015. Dual inhibition of PI3K and mTOR inhibits autocrine and paracrine proliferative loops in PI3K/Akt/mTOR-addicted lymphomas. Blood. 115(22): 4455-4463
97. Bhutto, Z. A., He, F., Zloh, M., Yang, J., Huang, J., Guo, T. and Wang, L. 2018. Use of quercetin in animal feed: effects on the P-gp expression and pharmacokinetics of orally administrated enrofloxacin in chicken. Scientific Reports. 8: 4400, doi: 10.1038/s41598-018-22354-1, 12 pages
98. Biaglow, J. E. and Durand, R. E. 1978. The enhanced radiation response of an in vitro tumour model by cyanide released from hydrolysed amygdalin. Int J Radiant Biol Relat Stud Phys Chem Med. 33(4): 397-401
99. Bikkavilli, R. K., Feigin, M. E. and Malbon, C. C. 2008. P38 mitogen-activated protein kinase regulates canonical Wnt-beta-catenin signaling by inactivation of GSK3beta. J Cell Sci. 121(Pt21): 3598-607, doi: 10.1242/jcs.032854
100. Billottet, C., Grandage, L. V., Gale, E. R., Quattropani, A., Rommel, C., Vanhaesebroeck, B. and Khwaja, A. 2006. A selective inhibitor of the p110 isoform of PI3-kinase inhibits AML cell proliferation and survival and increases the cytotoxic effects of VP16. Oncogene. 25(69): 6648-59
101. Blagden, S., Omlin, A., Josephs, D., Stavraka, C., Zivi, A., Pinato, D. J., Anthoney, A., Decorlova, S., Swales, K., Riisnaes, R., Pope, L., Noguchi, K., Shiokawa, R., Inatani, M., Prince, J., Jones, K., Twelves, C., Spicer, J. and Banerji, U. 2014. First-in-human study of CH5132799, an oral class I PI3K inhibitor, studying toxicity, pharmacokinetics, and pharmacodynamics, in patients with metastatic cancer. Clin Cancer Res. 20(23): 5908-17
102. Blain, S. W. 2018. Targeting p27 tyrosine phosphorylation as a modality to inhibit CDK4 and CDK2 and cause cell cycle arrest in breast cancer cells. Oncoscience. 5(5-6): 144-145, doi: 10.18632/oncoscience.427
103. Blain, W. S., Scher, I. H., Cordon-Cardo, C. and Koff, A. 2003. P27 as a target for cancer therapeutics. Cancer Cell. 3(2): 111-115

104. Blake, J. F., Xu, R., Bencsik, J. R., Xiao, D., Kallan, N. C., Schlachter, S., Mitchell, J. S., Spencer, K. L., Banka, A. L., Wallace, E. M., Gloor, S. L., Martinson, M., Woessner, R. D., Vigers, G. P., Brandhuber, B. J., Liang, J., Safina, B. S., Li, J., Zhang, B., Chabot, C., Do, S., Lee, L., Oeh, J., Sampath, D., Lee, B. B., Lin, K., Liederer, B. M. and Skelton, N. J. 2012. Discovery and preclinical pharmacology of a selective ATP-competetive Akt inhibitor (GDC-0068) for the treatment of human tumors. J Med Chem. 55(18): 8110-27

105. Bobe, G., Weinstein, J. S., Albanes, D., Hirvonen, T., Ashby, J., Taylor, R. P., Virtamo, J. and Stolzenberg-Solomon, Z. R. 2008. Flavonoid intake and risk of pancreatic cancer in male smokers (Finland). Cancer Epidemiology, Biomarkers and Prevention. 17(3): 553-62

106. Bohlke, K., Spiegelman, D., Trichopoulou, A., Katsouyanni, K. and Trichopoulos. 1999. Vitamins A, C and E and the risk of breast cancer: results from a case-control study in Greece. British Journal of Cancer. 79(1): 23-29, doi: 10.1038/sj.bjc.6690006

107. Böhm, F., Settergren, M. and Pernow, J. 2007. Vitamin C blocks vascular dysfunction and release of interleukin-6 induced by endothelin-1 in humans in vivo. Atherosclerosis. 190(2): 408-415

108. Bolarinwa, I. F., Orfila, C. and Morgan, MRA. 2014. Amygdalin content of seeds, kernels and food products commercially-available in the UK. Food Chemistry. 152.133-139. ISSN 0308-8146, https:// doi.org / 10.1016 / j. foodchem. 2013.11.002, 26 pages

109. Bolden, J. E., Peart, M. J. and Johnstone, R. W. 2006. Anticancer activities of histone deacetylase inhibitors. Nat Rev Drug Discov. 5(9): 769-84

110. Bombardier, C., Laine, L., Reicin, A., Shapiro, D., Burgos-Vargas, R., Davis, B., Day, R., Ferraz, M. B., Hawkey, C. J., Hochberg, M. C., Kvien, T. K., Schinitzer, T. J. and Weaver, A. 2000. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients wih rheumatoid arthritis. New England Journal of Medicine. 343(21): 1520-1528

111. Bon, J., Kahloon, R., Zhang, Y., Xue, J., Fuhrman, C. R., Tan, J., Burger, M., Kass, D. J., Csizmadia, E., Otterbein, L., Chandra, D., Bhargava, A., Pilewski, J. M., Roodman, G. D.,

Sciurba, F. C. and Duncan, S. R. 2014. Autoreactivity to glucose regulated protein 78 links emphysema and osteoporosis in smokers. PlosOne. 9(Issue 9): e105066, doi: 10.1371/journal.pone.0105066, 10 pages

112. Booth, N. L., Overk, C. R., Yao, P., Burdette, J. E., Nikolic, D., Chen, S., Bolton, J. L., van Breemen, R. B., Pauli, G. F. and Farnsworth, N. R. 2006. The chemical and biological profile of a red clover (*Trifolium pretense*) phase II clinical extract. J Altern Complement Med. 12(2): 133-139

113. Bostick, R. M., Potter, J. D., Sellers, T. A., Mckenzie, D. R., Kushi, L. H. and Folsom, A. R. 1993. Relation of calcium, vitamin D and dairy food intake to incidence of colon cancer among older women. American Journal of Epidemiology. 137 (12): 1302-1317

114. Bostrick, R. M., Potter, J. D., McKenzie, D. R., Sellers, T. A., Kushi, L. H., Steinmetz, K. A. and Folsom, A. R. 1993. Reduced risk of colon cancer with high intake of vitamin E: The Iowa women's health study. Cancer Research. 53(18): 4230-4237

115. Botterweck, A. A. M., van den Brandt, P. A. and Goldbohm, R. A. 2000. Vitamins, carotenoids, dietary fiber and risk of gastric carcinoma. Results from a prospective study after 6.3 years of follow up. Cancer. 88(4):737-748

116. Boutron, M. C., Faivre, J., Marteau, P., Couillault, C., Senesse, P. and Quipourt, V. 1996. Calcium, phosphorus, vitamin D, dairy products and colorectal carcinogenesis: a French case-control study. British Journal of Cancer. 74(1):145-151, PMID: 8679449

117. Brahimi-horn, M. C. and Pouyssegur, J. 2007. Hypoxia in cancer cell metabolism and pH regulation. Essays Biochem. 43:165-78, doi:10.1042/BSE0430165.

118. Brasky,M. T., Neuhouser, L. M., Cohn, E. D. and White, E. 2014. Associations of long-chain ω-3 fatty acids and fish intake with endometrial cancer risk in the vitamins and lifestyle cohort. Am J Clin Nutr. 99(3):599-608

119. Brennan, K. and Clarke, R. B. 2013. Combining Notch inhibition with current therapies for breast cancer treatment. Ther Adv Med Oncol. 5(1): 17-24, doi: 10.1177/1758834012457437

120. Brennan, M., Bhatti, H., Nerusu, K. C., Bhagavathula, N., Kang, S., Fisher, G. J., Varani, J. and Voorhees, J. J. 2003. Matrix metalloproteinase-1 is the major collagenolytic enzyme responsible for collogen damage in UV-irradiated human skin. Photochem Photobiol. 78(1): 43-8, PMID:12929747
121. Bretscher, A., Edwards, K. and Fehon, R. G. 2002. ERM proteins and merlin: integrators at the cell cortex. Nat Rev Mol Cell Biol. 3(8): 586-99
122. Bridge, G., Rashid, S. and Martin, S. A. 2014. DNA mismatch repair and oxidative DNA damage: implications for cancer biology and treatment. Cancers (Basel). 6(3): 1597-614
123. Bridges, D., Fisher, K., Zolov, S. N., Xiong, T., Inoki, K., Weisman, L. S. and Saltiel, A. R. 2012. Rab5 proteins regulate activation and localization of target of rapamycin complex 1. J Biol Chem. 287(25): 20913-21
124. Bromberg, J. and Wang, T. C. 2009. Inflammation and cancer: IL-6 and STAT3 complete the link. Cancer Cell. 15(2): 79-80
125. Broude, E. V., Demidenko, Z. N., Vivo, C., Swift, M. E., Davis, M. B., Blagosklonny, V. M. and Roninson, B. I. 2007. P21 (CDKN1A) is a negative regulator of p53 stability. Cell Cycle. 6(12): 1468-1471
126. Brüll, F., Mensink, R. P., Steinbusch, M. F., Husche, C., Lütjohann, D., Wesseling, G. and Plat, J. 2012. Beneficial effects of sitostanol on the attenuated immune function in asthma patients: Results of an in vitro approach. PlosOne. 7(10): e46895, doi: 10.1371/journal.pone.0046895, 10 pages.
127. Bubici, C. and Papa, S. 2014. JNK signaling in cancer: in need of new, smarter therapeutic targets. Br J Pharmacol. 171(1): 24-37, doi: 10.1111/bph.12432
128. Bublil, E. M. and Yarden, Y. 2007. The EGF receptor family: spearheading a merger of signaling and therapeutics. Curr Opin Cell Biol. 19(2): 124-34
129. Buchwald, S. Z. and Efstathiou, A. J. 2015. Re: MPDL3280A (Anti-PD-L1) treatment leads to chemical activity in metastatic bladder cancer. European Urology. 67(5): 975-975

130. Budni, J., Molz, S., Dal-Cim, T., Martin-de-Saavedra, M. D., Egea, J. and Lopez, M. G. 2018. Folic acid protects against glutamate-induced excitotoxicity in hippocampal slices through a mechanism that implicates inhibition of GSK-3B and iNOS. Molecular Neurobiology. 55(2): 1580-1589
131. Bumke-Vogt, C., Osterhoff, M. A., Borchert, A., Guzman-Perez, V., Sarem, Z., Birkenfeld, A. L., Bahr, V. and Pfeiffer, A. F. H. 2014. The flavons apigenin and luteolin induce Foxo1 translocation but inhibit gluconeogenic and lipogenic gene expression in human cells. Plus One. 9(8): e104321, doi:10.1371/journal.pone.0104321,16 pages
132. Bundock, E. A., Drummond, G. S. and Kappas, A. 1996. Tissue distribution of synthetic heme analogues: Studies with tin, chromium, and zinc mesoporphyrins. Pharmacology. 52(3): 187-98
133. Burri, B. J. 2014. Beta-cryptoxanthine as a source of vitamin A. J Sci Food Agric. 95: 1786-1794, doi: 10.1002/jsfa.6942
134. Burrows, N., Babur, M., Resch, J., Ridsdale, S., Mejin, M., Rowling, E. J., Brabant, G. and Williams, K. J. 2011. GDC-0941 inhibits metastatic characteristics of thyroid carcinomas by targeting both the phosphoinositide-3 kinase (PI3K) and hypoxia-inducible factor-1 α (HIF-1α) pathways. The Journal of Clinical Endocrinology and Metabolism. 96(12): E1934-E1943
135. Burstein, H. J., Sun, Y., Dirix, L. Y., Jiang, Z., Paridaens, R., Tan, A. R., Awada, A., Ranade, A., Jiao, S., Schwartz, G., Abbas, R., Powell, C., Turnbull, K., Vermette, J., Zacharchuk, C. and Badwe, R. 2010. Neratinib, an irreversible ErbB receptor tyrosine kinase inhibitor, in patients with advanced ErbB2-positive breast cancer. J Clin Oncol. 28(8): 1301-7
136. Bussolati, B., Ahmed, A., Pemberton, H., Landis, R. C., Di Carlo, F., Haskard, D. O. and Mason, J. C. 2004. Bifunctional role for VEGF-induced heme oxygenase-1 in vivo: induction of angiogenesis and inhibition of leukocytic infiltration. Blood. 103(3): 761-766
137. Cai, W. X., Liang, L., Wang, L., Han, J. T., Zhu, X. X., Han, H., Hu, D. H. and Zhang, P. 2014. Inhibition of Notch signaling

leads to increased intracellular ROS by up-regulating Nox4 expression in primary HUVECs. Cell Immunol. 287(2): 129-35

138. Cailleux, A., Subra, J. F., Riberi, P., Tuchais, E., Premel-Cabic, A. and Allain, P. 1988. Cyanide and thiocyanate blood levels in patients with renal failure or respiratory disease. J Med. 19(5-6): 345-51

139. Calder, P. C. and Yagoob, P. 1999. Glutamine and the immune system. Amino Acids. 17(3): 227-41

140. Campbell, K. J. and Tait, S. W. G. 2018. Targeting Bcl-2 regulated apoptosis in cancer. Open Biol. 8(5): 180002, doi: 10.1098/rsob.180002, 11 pages

141. Canales, M., Hernandez, T., Caballero, J., Romo de Vivar, A., Avilla, G., Duran, A. and Lira, R. 2005. Informant consensus factor and antibacterial activity of the medicinal plants used by the people of San Rafael Coxcatlan, Puebla, Mexico. J Ethnopharmacol. 97(3): 429-39

142. Candelario-Jalil, E., Akundi, R. S., Bhatia, H. S., Lieb, K., Appel, K., Munoz, E., Hüll, M. and Fiebich, B. L. 2006. Ascorbic acid enhances the inhibitory effect of aspirin on neuronal cyclooxygenase-2-mediated prostaglandin E2 production. J Neuroimmunol. 174(1-2): 39-51

143. Canfield, S. E., Zhu, K., Williams, S. A. and McConkey, D. J. 2006. Bortezomib inhibits docetaxel-induced apoptosis via a p21-dependent mechanism in human prostate cancer cells. Molecular Cancer Therapeutics. 5(8): 2043-2050

144. Cao, Y., Feng, Y., Zhang, Y., Zhu, X. and Jin, F. 2016. L-arginine supplementation inhibits the growth of breast cancer by enhancing innate and adaptive immune responses mediated by suppression of MDSCs in vivo. BMC Cancer. 16: 343, doi: 10.1186/s12885-016-2376-0, 11 pages

145. Cardama, G. A., Gonzalez, N., Maggio, J., Menna, P. L. and Gomez, D. E. 2017. Rho GTPases as therapeutic targets in cancer (Review). Int J Oncol. 51(4): 1025-1034

146. Cardus, A., Panizo, S., Encinas, M., Dolcet, X., Gallego, C., Aldea, M., Fernandez, E. and Valdivielso, J. M. 2009. 1.25-dihydroxyvitamin D3 regulates VEGF production through a vitamin D response element in the VEGF ptomoter.

Atherosclerosis. 204 (1): 85-9, doi: 10.1016 / j.atherosclerosis. 2008.08.020

147. Carew, J. S., Espitia, C. M., Zhao, W., Kelly, K. R., Coffey, M., Freman, J. W. and Nawrocki, S. T. 2013. Reolysin is a novel reovirus-based agent that induces endoplasmic reticular stress-mediated apoptosis in pancreatic cancer. Cell Death and Disease. 4: e728, doi: 1038/cddis.2013.259, 11 pages

148. Cargnello, M. and Roux, P. P. 2011. Activation and function of the MAPKs and their substrates, the MAPK-Activated Protein Kinases. Microbial Mol Biol Rev. 75(1): 50-83, doi: 10.1128/ MMBR.00031-10

149. Carpenter, R. L. and Lo, H. 2016. Regulation of apoptosis by Her2 in breast cancer. J Carcinog Mutagen. 2013 (Suppl 7):003, doi:10.4172/2157-2518.S7-003, 13 pages

150. Carter, G. L., D'Orazio, A. J. and Pearson, J. K. 2014. Resveratrol and cancer: focus on in vivo evidence. Endocr Relat Cancer. 21(3): R209-R225, doi: 10.1530/ERC-13-0171

151. Cartwright, T. A., Campos, C. R., Cannon, R. E. and Miller, D. S. 2013. MRP1 is essential for sphingolipid signaling to p-glycoprotein in mouse blood-brain and blood-spinal cord barriers. J Cereb Blood Flow Metab. 33(3): 381-388

152. Casara, P., Davidson, J., Claperon, A., Le Toumelin-Braizat, G., Vogler, M., Bruno, A., Chanrion, M., Lysiak-Auvity, G., Le Diguarher, T., Starck, J. B., Chen, I., Whitehead, N., Graham, C., Matassova, N., Dokurno, P., Pedder, C., Wang, Y., Qiu, S., Girard, A. M., Schneider, E., Grave, F., Studeny, A., Guasconi, G., Rocchetti, F., Maiga, S., Henlin, J. M., Colland, F., Kraus-Berthier, L., Le Gouill, S., Dyer, M. J. S., Hubbard, R., Wood, M., Amiot, M., Cohen,G. M., Hickman, J. A., Morris, E., Murray, J. and Geneste, O. 2018. S55746 is a novel orally active Bcl-2 selective and potent inhibitor that impairs hematological tumor growth. Oncotarget. 9(28): 20075-20088

153. Castro, A. F. and Altenberg, G. A. 1997. Inhibition of drug transport by genistein in multidrug-resistant cells expressing P-glycoprotein. Biochemical Pharmacology. 53(1):89-93, https:// doi.org/10.1016/S0006-2952(96)00657-0

154. Catani, M. V., Rossi, A., Costanzo, A., Sabatini, S., Levrero, M., Melino, G. and Avigliano, L. 2001. Induction of gene expression via activator protein-1 in the ascorbate protection against UV-induced damage. Biochemical Journal. 356(Pt1): 77-85, doi: 10.1042/0264-6021:3560077

155. Cervello, M., Bachvarov, D., Lampiasi, N., Cusimano, A. and Azzolina, A. 2013. Novel combination of sorafenib and Celecoxib provides synergistic anti-proliferative and pro-apoptotic effects in human liver cancer cells. PlosOne. 8(6): e65569, doi: 10.1371/journal.pone.0065569, 16 pages.

156. Cervello, M., Bachvarov, D., Lampiasi, N., Cusimano, A., Azzolina, A., McCubrey, A. J. and Montalto, G. 2012. Molecular mechanisms of sorafenib action in liver cancer cells. Cell Cycle. 11(15): 2843-2855

157. Cha, J. H., Kim, K. W., Ha, W. A., Kim, H. M. and Chang, J. M. 2017. Anti-inflammatory effect of lycopene in SW480 human colorectal cancer cells. Nutr Res Pract. 11(2): 90-96

158. Chae, Y., Cho, K. H., Yoon, I., Noh, C., Lee, H., Park, Y., Ji, E., Seo, M. and Maeng, H. 2016. Vitamin D receptor-mediated upregulation of CYP3A4 and MDR1 by quercetin in Caco-2 cells. Planta Medica. 82: 121-130, doi: 1055/s-0035-1557898

159. Chaiprasongsuk, A., Lohakul, J., Soontrapa, K., Sampattavanich, S., Akarasereenont, P. and Panich, U. 2017. Activation of Nrf2 reduces UVA-mediated MMP-1 upregulation via MAPK/AP-1 signaling cascades: the photoprotective effects of sulforaphane and hispidulin. Journal of Pharmacology and Experimental Therapeutics. 362:2, Doi: 10.1124/jpet.116.238048, 43 pages

160. Chalhoub, N. and Baker, J. S. 2009. PTEN and the PI3-kinase pathway in cancer. Annu Rev Pathol. 4:127-150, doi:10.1146/annurev.pathol.4.110807.092311

161. Chan, J. M., Stampfer, M. J., Ma, J., Rimm, E. B., Willett, W. C. and Giovannucci, E. L. 1999. Supplemental vitamin E intake and prostate cancer risk in a large cohort of men in the United States. Cancer Epidemiol Biomarkers Prev. 8(10): 893-899

162. Chan, K. T., Li, K., Liu, S. L., Chu, K. H., Toh, M. and Xie, W. D. 2010. Cucurbitacin B inhibits STAT3 and the Raf/MEK/ERK

pathway in leukemia cell line K562. Cancer Letters. 289(1): 46-52, doi: 10.1016/j.canlet.2009.07.015

163. Chan, M. M., Fong, D., Soprano, K. J., Holmes, W. F. and Heverling, H. 2003. Inhibition of growth and sensitization to cisplatin-mediated killing ovarian cancer cells by polyphenolic chemopreventive agents. J Cell Physiol. 194(1): 63-70, doi:10.1002/jcp.10186

164. Chang, C. 2011. The role of MAPK pathway in CD4T cell proliferation and differentiation. UC San Diego, Pro Quest ID: Chang_ucsd_0033D_11964. Merritt ID: ark:/20775/bb89774415. Retriewed from https://escholarship.org/uc/item/6tb5b89q

165. Chang, H. K., Shin, M. S., Yang, H. Y., Lee, J. W., Kim, Y. S., Lee, M. H., Kim, J., Kim, K. H. and Kim, C. J. 2006. Amygdalin induces apoptosis through regulation of Bax and Bcl-2 expressions in human DU145 and LNCaP prostate cancer cells. Biol Pharm Bull. 29(8): 1597-602

166. Chang, H. P., Wang, M. L., Hsu, C. Y., Liu, M. E., Chan, M. H. and Chen, Y. H. 2011. Suppression of inflammation-associated factors by indole-3-carbinol in mice fed high-fat diets and in isolated, co-cultured macrophages and adipocytes. International Journal of Obesity. 35(12): 1530-1538

167. Chang, P., Walker, M. C. and Williams, R. S. B. 2014. Seizure-induced reduction in PIP3 levels contributes to seizure-activity and is rescued by valproic acid. Neurobiol Dis. 62(100):296-306

168. Chang, Y., Huang, Y., Li, Z. and Chen, C. 2012. GRP78 knockdown enhances apoptosis, via the down-regulation of oxidative stress and Akt pathway after Epirubicin treatment in colon cancer DLD-1 cells. Plos One. 7:4, e.35123, 11 pages, doi: 10.1371/journal.pone.0035123

169. Chanmugam, P., Feng, L., Liou, S., Jang, B. C., Boudreau, M., Yu, G., Lee, J. H., Kwon, H. J., Beppu, T., Yoshida, M., Xia, Y., Wilson, B. C. and Hwang, D. 1995. Radicicol, a protein tyrosine kinase inhibitor suppresses the extension of mitogen-inducible cyclooxygenase in macrophages stimulated with lipopolysaccharide and in experimental glomerulonephritis. The Journal of Biological Chemistry. 270: 5418-5426, doi: 10.1074/jbc.270.10.5418

170. Chantranupong, L., Scaria, S. M., Saxton, R. A., Gygi, M. P., Shen, K., Wyant, G. A., Wang, T., Harper, J. W., Gygi, S. P. and Sabatini, D. M. 2016. The Castor proteins are arginine sensors for the mTORC1 pathway. 165(1): P153-164, https://doi.org/10.1016/j.cell.2016.02.035

171. Charrez, B., Qiao, L. and Hebbard, L. 2015. The role of fructose in metabolism and cancer. Horm Mol Biol Clin Invest. 22(2): 79-89

172. Chatterjee, D. and Bhattacharfee, P. 2015. Use of eugenol-lean clove extract as a flavoring agent and natural antioxidant in mayonnaise: product characterization and storage study. J Food Sci Technol. 52(8): 4945-4954

173. Chawla-Sarkar, M., Lindner, D. J., Liu, Y. F., Williams, B. R., Sen, G. C., Silverman, R. H. and Borden, E. C. 2003. Apoptosis and interferons: role of interferon-stimulated genes as mediators of apoptosis. Apoptosis. 8(3): 237-49

174. Chemnitz, J. M., Parry, R. V., Nichols, K. E., June, C. H. and Riley, J. L. 2004. SHP-1 and SHP-2 associate with immunoreceptor tyrosine-based switch motif of programmed death 1 upon primary human T cell stimulation, but only receptor ligation prevents T cell activation. Journal of Immunology. 173(2): 945-54

175. Chen, B., Dodge, E. M., Tang, W., Lu, J., Ma, Z., Fan, C., Wei, S., Hao, W., Kilgore, J., Williams, N. S., Roth, G.M., Amatruda, F. J., Chen, C. and Lum, L. 2009. Small molecule-mediated distruption of Wnt-dependent signaling in tissue regeneration and cancer. Nat Chem Biol. 5(2): 100-107

176. Chen, C., Peng, W., Tsai, K. and Hsu, S. 2007. Luteolin suppresses inflammation-associated gene-expression by blocking NF-kB and AP-1 activation pathway in mouse alveolar macrophages. Life Sciences. 81 (Issues 23-24):1602-1614, https: // doi.org /10.1016 / j. lfr. 2007.09.028

177. Chen, F., Li, Q., Yu, Y., Yang, W., Shi, F. and Qu, Y. 2015. Association of vitamin C, vitamin D, vitamin E and risk of bladder cancer: a dose-response meta-analysis. Scientific Reports. 5: 9599, doi: 10.1038/srep09599, 7 pages

178. Chen, G., Xu, X., Zhang, L., Fu, Y., Wang, M., Gu, H. and Xie, X. 2014. Blocking autocrine VEGF signaling by sunitinib, an anti-cancer drug, promotes embryonic stem cell self-renewal and somatic cell reprogramming. Cell Research. 24(9): 1121-1136
179. Chen, H. Y., Ren, X. Y., Wang, W. H., Zhang, Y. X., Chen, S. F., Zhang, B. and Wang, L. X. 2014. Upregulated ROS production induced by the proteasome inhibitor MG-132 on XBP1 gene expression and cell apoptosis in Tca-8113 cells. Biomed Pharmacother. 68(6): 709-13
180. Chen, H., Shien, K., Suzawa, K., Tsukuda, K., Tomida, S., Sato, H., Torigoe, H., Watanabe, M., Namba, K., Yamamoto, H., Soh, J., Asano, H., Miyoshi, S. and Toyooka, S. 2017. Elacridar, a third-generation ABCB1 inhibitor, overcomes resistance to docetaxel in non-small cell lung cancer. Oncol Lett. 14(4): 4349-4354
181. Chen, J. 2012. Targeted therapy of obesity-associated colon cancer. Transl Gastrointest Cancer. 1(1): 44-57, doi: 10.3978/j.issn.2224-4778.2011.11.01
182. Chen, J. and Stinski, F. M. 2002. Role of regulatory elements and MAPK/ERK or p38 MAPK pathways for activation of human cytomegalovirus gene expression. J Virol. 76(10):4873-4885
183. Chen, J., Liu, K., Liu, Y., Wang, X. and Zhang, Z. 2019. Targeting mTORC1/2 with OSI.027 inhibits proliferation and migration of keloid keratinocytes. Exp Dermatol. 28(3): 270-275
184. Chen, K., Hsu, W., Ho, J., Lin, C., Chu, C., Kandaswami, C. C., Lee, M. and Cheng, C. 2018. Flavonoids luteolin and quercetin inhibit RPS19 and contributes to metastasis of cancer cells through c-Myc reduction. Journal of Food and Drug Analyhsis. 26(3): 1180-1191
185. Chen, M., Lin, Y., Yang, C. and Hu, M. 2012. Lycopene inhibits angiogenesis both in vitro and in vivo by inhibiting MMP-2/uPA system through VEGFR-2-mediated PI3K-Akt and ERK/p38 signaling pathway. Molecular Nutrition and Food Research. 56(6): 889-899
186. Chen, M., Wang, J., Lu, J., Bond, M. C., Ren, X., Lyerly, H. K., Barak, L. S. and Chen, W. 2009. The anti-helmintic

niclosamide inhibits Wnt/Frizzled1 signaling. Biochemistry. 48(43): 10267-10274

187. Chen, P., Xu, S. and Qu, J. 2017. Lycopene protects keratinocytes against UVB radiation-induced carcinogenesis via negative regulation of Foxo3a through the mTORC2/Akt signaling pathway. J Cell Biochem. 19: 366-377, doi:10.1002/jcb.26189

188. Chen, W., Wang, Y., Zhao, A., Xia, L., Xie, G., Su, M., Zhao, L., Liu, J., Qu, C., Wei, R., Rajani, C., Ni, Y., Cheng, Z., Chen, Z., Chen, S. and Jia, W. 2016. Enhanced fructose utilization mediated by SLC2A5 is a unique metabolic feature of acute myeloid leukemia with therapeutic potential. Cancer Cell. 30(5): 779-791

189. Chen, X., Ren, K., He, H. and Shao, R. 2008. Involvement of PI3K/AKT/GSK3β pathway in tetrandrine-induced G1 arrest and apoptosis. Cancer Biology and Therapy. 7(7): 1073-1078

190. Chen, X., Yang, G., Song, J., Xu, H., Li, D., Goldsmith, J., Zeng, H., Parsons-Wingerter, P. A., Reinecker, H. and Kelly, C. P. 2013. Probiotic yeast inhibits VEGFR signaling and angiogenesis in intestinal inflammation. PlosOne. 8(5): e64227, do: 10.1371/journal.pone.0064227, 7 pages

191. Chen, X., Zhao, M., Hao, M., Sun, X., Wang, J., Mao, Y., Zu, L., Liu, J., Shen, Y., Wang, J. and Shen, K. 2013. Dual inhibition of PI3K and mTOR mitigates compensatory AKT activation and improves tamoxifen response in breast cancer. Mol Cancer Res. 11(10): 1269-78

192. Chen, Y., Ma, J., Wang, F., Hu, J., Cui, A., Wei, C., Yang, Q. and Li, F. 2013. Amygdalin induces apoptosis in human cervical cancer cell line HeLa cells. Immunopharmacol Immunotoxicol. 35(1): 43-51, doi: 10.3109/08923973.2012.738688.

193. Chen, Y., Wang, X., Zhang, Q., Zhu, J., Li, Y., Xie, C., Li, X., Wu, J., Geng, S., Zhong, C. and Han, H. 2017. (-)-Epigallocatechin-3-Gallate inhibits colorectal cancer stem cells by suppressing Wnt/β-catenin pathway. Nutrients. 9(6): 572, doi: 10.3390/nu9060572, 11 pages

194. Chen, Z., Huang, C., Yang, Y. L., Ding, Y., Ou-Yang, H. Q., Zhang, Y. Y. and Xu, M. 2012. Inhibition of the STAT3 signaling

pathway is involved in the antitumor activity of cepharanthine in SaOS2 cells. Acta Pharmacol Sin. 33(1): 101-8, doi: 10.1038/aps.2011.164

195. Cheng, C. K., Gustafson, W. C., Charron, E., Houseman, B. T., Zunder, E., Goga, A., Gray, N. S., Pollok, B., Oakes, S. A., James, C. D., Shokat, K. M., Weiss, W. A. and Fan, Q. W. 2012. Dual blockade of lipid and cyclin-dependent kinase induces lethality in malignant glioma. Proc Natl Acad Sci USA. 109(31): 12722-7

196. Cheng, C. Y., Ho, T. Y., Hsiang, C. Y., Tang, N. Y., Hsieh, C. L., Kao, S. T. and Lee, Y. C. 2017. *Angelica sinensis* exerts angiogenic and anti-apoptotic effects against cerebral ischemia-reperfusion injury by activating p38MAPK/HIF-1[Formula:see text]/VEGF-A signaling in rats. Am J Chin Med. 45(8): 1683-1708

197. Cheng, T. D., Barnett, J. M., Kristal, R. A., Ambrosone, B. C., King, B. I., Thornquist, D. M., Goodman, E. G. and Neuhouser, L. M. 2011. Genetic variation in myeloperoxidase modifies the association of serum α-tocopherol with aggressive prostate cancer among current smokers. J Nutr. 141(9): 1731-1737

198. Cheng, Y. W., Liao, L. D., Yang, Q., Chen, Y., Nie, P. J., Zhang, X. J., Xie, J. J., Shan, B. E., Zhao, L. M., Xu, L. Y. and Li, E. M. 2018. The histone deacetylase inhibitor panobinostat exerts anticancer effect on esophageal squamous cell carcinoma cells by inducing cell cycle arrest. Cell Biochem Funct. 36(8): 398-407

199. Chetram, A. M. and Hinton, V. C. 2012. PTEN regulation of ERK1/2 signaling in cancer. J Recept Signal Transduct Res. 32(4):190-195

200. Chew, Y. C., Adhikary, G., Wilson, G. M., Xu, W. and Eckert, R. 2012. Sulforaphane induction of $p21^{Cip1}$ cyclin-dependent kinase inhibitor expression requires p53 and Sp1 transcription factors and Is p53 dependent. J Biol Chem. 287(20): 16168-16178

201. Chewchuk, S., Boorman, T., Edwardson, D. and Parissenti, A. M. 2018. Doxorubicin sensitivity in ABCC1-expressing tumour cells. Scientific Reports. 8: 5413, doi: 10.1038/s41598-018-23496-y, 11 pages

202. Chi, X., Zhang, T., Chu, X., Zhen, J. and Zhang, D. 2018. The regulatory effect of genistein on granulosa cell in ovary of rat with PCOS through Bcl-2 and Bax signaling pathways. J Vet Med Sci. 80(8): 1348-1355
203. Chian, S., Thapa, R., chi, Z., Wang, J. and Tang, X. 2014. Luteolin inhibits the Nrf2 signaling pathway and tumor growth in vivo. Biochemical and Biophysical Research Communications. 447(4): 602-608
204. Chien, M. H., Ku, C. C., Johansson, G., Chen, M. W., Hsiao, M., Su, J. L., Inou, H., Hua, K. T., Wei, L. H. and Kuo, M. L. 2009. Vascular endothelial growth factor-C (VEGF-C) promotes angiogenesis by induction of COX-2 in leukemic cells via the VEGF-R3/JNK/AP-1 pathway. Carsinogenesis. 30(12): 2005-13
205. Chiou, J. F., Taii C.J., Huang, M.T., Wei, P.L., Wang, Y,H., An, J., Wu, C, H., Liu, T. Z. and Chang YJ. 2010. Glucose-regulated protein 78 is a novel contributor to acquisition of resistance to sorafenib in hepatocellular carcinoma. Ann Surg Oncol. 17(2):603-12. doi: 10.1245/s10434-009-0718-8
206. Chitnis, P. M., Adwankar, K. M. and Amonkar, J. A. 1985. Studies on high-dose chemotherapy of amygdalin in murine P388 lymphocytic leukemia and P815 mast cell leukemia. J Cancer Res Clin Oncol. 109(3): 208-9
207. Cho, S., Lu, M., He, X., Ee, P. R., Bhat, U., Schneider, E., Miele, L. and Beck, W. T. 2011. Notch 1 regulates the expression of the multidrug resistance gene ABCC1/MRP1 in cultured cancer cells. Proc Natl Acad Sci USA. 108(51): 20778-20783
208. Choi, S., Youn, J., Kim, K., Jao, D. H., Shin, S., Lee, J., Lee, H. K., An, I., Kwon, S., Youn, H. J., Ahn, J. K. and Cha, H. J. 2016. Apigenin inhibits UVA-induced cytotoxicity in vitro and prevents signs of skin aging in vivo. International Journal of Molecular Medicine. 38(2): 627-634
209. Choi, W. Y., Choi, B. T., Lee, W. H. and Choi, Y. H. 2008. Sulforaphane generates reactive oxygen species leading to mitochondrial perturbation for apoptosis in human leukemia U937 cells. Biomedicine and Pharmacotherapy. 62(9): 637-644

210. Choudhury, A., Chakraborty, I., Banerjee, T. S., Vana, D. R. and Adapa, D. 2017. Efficacy of morin as a potential therapeutic phytocomponent: Insights into the mechanism of action. International Journal of Medical Research & Health Sciences. 6(11): 175-194

211. Chresta, C. M., Davies, B. R., Hickson, I., Harding, T., Cosulich, S., Critchlow, S. E., Vincent, J. P., Ellston, R., Jones, D., Sini, P., James, D., Howard, Z., Dudley, P., Hughes, G., Smith, L., Maguire, S., Hummersone, M., Malagu, K., Menear, K., Jenkins, R., Jacopsen, M., Smith, G. C., Guichard, S. and Pass, M. 2010. AZD8055 is a potent, selective and orally bioavailable ATP-competitive mammalian target of rapamycin kinase inhibitor with in vitro and in vivo antitumor activity. Cancer Res. 70: 288-98, doi: 10.1158/0008-5472

212. Christman, J. K., Sheikhnejad, G., Dizik, M., Abileah, S. and Wainfan, E. 1993. Reversibility of changes in nucleic acid methylation and gene expression induced in rat liver by severe dietary methyl deficiency. Carcinogenesis. 14(4): 551-7

213. Chu, I., Blackwell, K., Chen, S. and Slingerland, J. 2005. The dual ErbB1/ErbB2 inhibitor, lapatinib (GW572016), cooperates with tamoxifen to inhibit both cell proliferation-and estrogen-dependent gene expression in antiestrogen-resistant breast cancer. Cancer Res. 65(1): 18-25, PMID:15665275

214. Chung, M., Kim, D., Na, H., Kim, J., Kim, H., Haegeman, G. and Syrh, Y. 2014. Genistein inhibits phorbol ester-induced NF-kB transcriptional activity and COX-2 expression by blocking the phosphorylation of p65/RelA in human mammary epithelial cells. Mutation Research/Fundemental and Molecular Mechanisms of Mutagenesis. 768:74-83, https: //doi.org/10.1016/j. mrfmmm.2014.04.003

215. Cianciulli, A., Salvatore, R., Porro, C., Trotta, T. and Panaro, M. A. 2016. Folic acid is able to polarize the inflammatory response in LPS activated microglia by regulating multiple signaling pathways. Mediators Inflamm. 2016: 5240127, doi: 10.1155/2016/5240127, 10 pages

216. Ciarcia, R., Vitiello, M. T., Galdiero, M., Pacilio, C., Iovano, V., d'Angelo, D., Pagnini, D., Caparrotti, G., Conti, D., Tomei, V., Florio, S. and Giordano, A. 2012. Imatinib treatment inhibit IL-8, NF-kB and AP-1 production and modulate intracellular calcium in CML patients. J Cell Physiol. 227(6): 2798-803

217. Ciorba, M. A., Riehl, E. T., Rao, M. S., Moon, C., Ee, X., Nava, G. M., Walker, M. R., Marinshaw, J. M., Stappenbeck, T. S. and Stenson, W. F. 2012. *Lactobacillus* probiotic protects intestinal epithnelium from radiation injury in a TLR-2/cyclo-oxygenase-2-dependent manner. Gut. 61: 829-838, doi: 10.1136/gutjnl.2011.300367

218. Cipolla, B. G., Mandron, E., Lefort, J. M., Coadou, Y., Della Negra, E., Corbel, L., Le Scodan, R., Azzouzi, A. R. and Mottet, N. 2015. Effect of sulforaphane in men with biochemical recurrence after radical prostatectomy. Cancer Prev Res (Phila). 8(8): 712-9

219. Cipollone, R., Ascenzi, P., Tomao, P., Imperi, F. and Visca, P. 2008. Enzymatic detoxification of cyanide: clues from Pseudomonas aeruginosa Rhodanese. J Mol Microbial Biotechnol. 15(2-3): 199-211

220. Clarke, D. B., Lloyd, A. S. and Bailey, V. A. 2008. Determination of phytoestrogens in dietary supplements by LC-MS/MS. Food Additives and Contaminants. 25(05): 534-547

221. Clarke, L.H., Clarke, C.R. and Lippman, M. 1999. The influence of maternal diet on breast cancer risk among female offspring. Nutrition. 15(5): 392–401.

222. Cohen-Lahav, M., Shany, S., Tobvin, D., Chaimovitz, C. and Douvdevani, A. 2006. Vitamin D decreases NF-kB activity by increasing Ikβα levels. Neprhology Dialysis Transplantation. 21(4): 889-897

223. Cole, A. L. 2009. New discoveries on the biology and detection of human chorionic gonadotropin. Reprod Biol Endocrinol. 7: 8, doi: 1186/1477-7827-7-8, 37 pages

224. Collins, T., Read, M. A., Neish, A. S., Whitley, M. Z., Thanos, D. and Maniatis, T. 1995. Transcriptional regulation of endothelial cell adhesion molecules: NF-kappaB and cytokine-inducible enhancers. FASEB J. 9(10): 899-909

225. Coombs, M. R. P., Harrison, M. E. and Hoskin, D. W. 2016. Apigenin inhibits the inducible expression of programmed death ligand1 by human and mouse mammary carcinoma cells. Cancer Letters. 380(2): 424-433

226. Coqueret, O. 2003. New roles for p21 and p27 cell-cycle inhibitors: a function for each cell compartment. Trends in Cell Biology. 13(2): 65-70

227. Corral, L. G., Haslett, P. A., Muller, G. W., Chen, R., Wong, L. M., Ocampo, C. J., Patterson, R. T., Stirling, D. I. and Kaplan, G. 1999. Differential cytokine modulation and T cell activation by two distinct classes of thalidomide analogues that are potent inhibitors of TNF-alpha. J Immunol. 163(1): 380-6, http://www.jimmunol.org/content/163/1/380

228. Corriveau, C. C., Madara, P. J., Van Dervort, A. L., Tropea, M. M., Wesley, R. A. and Danner, R. L. 1998. Effects of nitric oxide on chemotaxis and endotoxin-induced interleukin-8 production in human neutrophils. J Infect Dis. 177(1): 116-26, PMID:9419178

229. Couch, A. J., Zhang, G., Beyer, C. J., de Zafra, Z. L., Gupta, P., Kamath, V. A., Lewin-Koh, N., Tarrant, J., Allamneni, P. K., Cain, G., Yee, S., Ross, S., Cook, R., Tasi, S. P., Ruppel, J., Ridgway, J. B., Paluch, M., Hass, E. P., Franklin, J. and Yan, M. 2016. Balancing efficacy and safety of an anti-DLL4 antibody through pharmacokinetic modulation. Clinical Cancer Research. 20: 2015, doi: 10.1158/1078-0432.CCR-15-1380, 11 pages

230. Crane, C., Panner, A., Pieper, R. O., Arbiser, J. and Parsa, A. T. 2009. Honokiol-mediated inhibition of PI3K/mTOR pathway: a potential strategy to overcome immunoresistance in glioma, breast, and prostate carcinoma without impacting T cell function. J Immunother. 32(6): 585-92

231. Crawford, S., Belajic, D., Wei, J., Riley, P. J., Dunford, J. P., Bembenek, S., Fourie, A., Edwards, P. J., Karlsson, L., Brunmark, A., Wolin, L. R. and Blevitt, M. J. 2008. A novel B-RAF inhibitor blocks interleukin-8 (IL-8) synthesis in human melanoma xenografts, revealing IL-8 as a potential pharmacodynamic biomarker. Mol Cancer Ther. 7(3): 492-9

232. Crowley, V. M., Huard, D. J. E., Lieberman, R. L. and Blagg, B. S. J. 2017. Second generation Grp94-selective inhibitors provide opportunities for the inhibition of metastatic cancer. Chem Eur J. 23: 15775-15782, doi: 10.1002/chem.201703398
233. Croxtall, J. D., van Hal, P. T., Choudhury, Q., Gilroy, D. W. and Flower, R. J. 2002. Different glucocorticoids vary in their genomic and non-genomic mechanism of action in A549 cells. Br J Pharmacol. 135(2): 511-519
234. Cui, R., Liu, Z. and Xu, Q. 2014. Blood, α-tocopherol levels and risk of prostate cancer: A meta-analysis of prospective studies. Plos One. 9(3): e9304. Doi: 10.1371/journal.pone.0093044, 7 pages.
235. Cui, S., Li, W., Wang, P., Lv, X., Gao, Y. and Huang, G. 2018. Folic acid inhibits homocyteine-induced cell apoptosis in human umbilical vein endothelial cells. Molecular and Cellular Biochemistry. 444(Issue 1-2): 77-86, https://doi.org/10.1007/s11010-017-3232-5
236. Cui, Y., Xing, P., Wang, Y., Liu, M., Qiu, L., Ying, G. and Li, B. 2017. NADPH accumulation is responsible for apoptosis in breast cancer cells induced by fatty acid synthase inhibition. Oncotarget. 8(20): 32576-32585
237. Curro, M., Gugliandolo, A., Gangemi, C., Risitano, R., Ientile, R. and Caccamo, D. 2014. Toxic effects of mildly elevated homocyteine concentrations in neuronal-like cells. Neurochem Res. 39(8): 1485-95
238. D'Alessandro, A., Amelio, I., Berkers, C. R., Antonov, A., Vousden, K. H., Melino, G. and Zolla, L. 2014. Metabolic effect of Tap63α: enhanced glycolysis and pentose phosphate pathway, resulting in increased antioxidant defense. Oncotarget. 5(17): 7722-33
239. D'Eliseo, D. and Velotti, F. 2016. Omega 3 fatty acids and cancer cell cytotoxicity: Implications for multi-targeted cancer therapy. J Clin Med. 5(2): 15
240. Dahiya, N., Sherman-Baust, C. A., Wang, T. L., Davidson, B., Shih, I., Zhang, Y., Wood, W., Becker, K. G. ad Morin, P. J. 2008. MicroRNA expression and identification of putative

mRNA targets in ovarian cancer. Plos One. 3(6): e2436, doi: 10.1371/journal.pone.0002436, 11 pages

241. Dai, C., Zhang, B., Liu, X., Ma, S., Yang, Y., Yao, Y., Feng, M., Bao, X., Li, G., Wang, J., Guo, K., Ma, W., Xing, B., Lian, W., Xiao, J., Cai, F., Zhang, H. and Wang, R. 2013. Inhibition of PI3K/AKT/mTOR pathway enhances temozolomide-induced cytotoxicity in pituitary adenoma cell lines in female nude mice. Endocrinology. 154(3): 2247-59

242. Dai, G., Zheng, D., Wang, Q., Yang, J., Liu, G., Song, Q., Sun, X., Tao, C., Hu, Q., Gao, T., Yu, L. and Guo, W. 2017. Baicalein inhibits progression of osteosarcoma cells through inactivation of the Wnt/β-catenin signaling pathway. Oncotarget. 8(49): 86098-86116

243. Dai, L., Liu, Z., Liang, W., Yao, Y., Xu, J., Ye, D., Zou, L. and Shen, Y. 2015. Effect of vitamin C on apoptosis of nucleus pulposus cells induced by tumor necrosis factor a and serum deprivation. Zhongguo Xiu Fu Chong Jian Wai Ke Za Zhi. 29(4): 490-7

244. Dallaglio, K., Bruno, A., Cantelmo, A. R., Esposito, A. I., Ruggiero, L., Orecchioni, S., Calleri, A., Bertolini, F, Pfeffer, U., Noonan, D. M. and Albini, A. 2014. Paradoxic effects of metformin on endothelial cells and angiogenesis. Carciogenesis. 35(5): 1055-66

245. Dameron, K. M., Volpert, O. V., Tainsky, M. A. and Bouck, N. 1994. Control of angiogenesis in fibroblasts by p53 regulation of thrombospondin-1. Science. 265(5178): 1582-4

246. Damjanov, N., Kauffman, R. S. and Spencer-Green, G. T. 2009. Efficacy, pharmacodynamics, and safety of VX-702, a novel p38 MAPK inhibitor, in rheumatoid arthritis: results of two randomized, double-blind, placebo-controlled clinical studies. Arthritis Theum. 60(5): 1232-41

247. Dan, H. C., Cooper, M. J., Cogswell, P. C., Duncan, J. .A., Ting, J. P. Y. and Baldwin, A. S. 2008. Akt-dependent regulation of NF-kB is controlled by mTOR and Raptor in association with IKK. Genes Dev. 22(11): 1490-1500

248. Dang, C. V. 2012. Links between metabolism and cancer. Genes Dev. 26(9): 877-90

249. Dartigues, J., Dabis, F., Gros, N., Moise, A., Bois, G., Salamon, R., Dilhuydy, J. and Courty, G. 1990. Dieatry vitamin A, beta carotene and risk of epidermoid lung cancer in south-western France. Eur J Epidemiol. 6(3): 261-265

250. Das, T. P., Suman, S., Alatassi, H., Ankem, M. K. and Damodaran, C. 2016. Inhibition of Akt promotes Foxo3a - dependent apoptosis in prostate cancer. Cell Death & Disease. 7: e2111, doi: 10.1038 / cddis. 2015.403, 10 pages

251. Daviglus, M. L., Dyer, A. R., Persky, V., Chavez, N., Drum, M., Goldberg, J., Liu, K., Morris, D. K., Shekelle, R. B. and Stamler, J. 1996. Dietary beta-carotene, vitamin C and risk of prostate cancer: results from the western electric study. Dietary antioxidants and prostate cancer. 7(5):472-476

252. Davis, C. D., Zeng, H. and Finley, J. W. 2002. Selenium-enriched broccoli decreases tgumorigenesis in multiple intestinal neoplasia mice. J Nutr. 132(2):307-9

253. Davis, R., Singh, K. P., Kurzrock, R. and Shankar, S. 2009. Sulforaphane inhibits angiogenesis through activation of Foxo transcription factors. Oncology Reports. 22:1473-1478, https:// doi.org/10.3892/or_00000589

254. De Barros, S., Zakaroff-Girard, A., Lafontan, M., Galitzky, J. and Bourlier, V. 2007. Inhibition of human preadipocyte proteasomal activity by HIV protease inhibitors or specific inhibitor lactacystin leads to a defect in adipogenesis, which involves matrix metalloproteinase-9. J Pharmacol Exp Ther. 320(1): 291-9, doi:10.1124/jpet.106.111849

255. De Marco, S., Sichetti, M., Muradyan, D., Piccioni, M., Traina, G., Pagiotti, R. and Pietrella, D. 2018. Probiotic cell-free supernatants exhibited anti-inflammatory and antioxidant activity on human gut epithelial cells and macrophages stimulated with LPS. Evidence-Based Complementary and Alternative Medicine. Volume 18, Article ID1756308, 12 pages, https://doi.org/10.1155/2018/1756308

256. De Melo, O. G., Malvar, D. C., Vanderlinde, F. A., Rocha, F. F., Pires, P. A., Costa, E. A., Matos, L. G., Kaiser, C. R. and Costa, S. S. 2009. Antinociceptive and anti-inflammatory

kaempferol glycosides from Sedum dendroideum. Journal of Ethnopharmacology. 124(2): 228-232

257. De Santi, M., Galluzzi, L., Lucarini, S., Paoletti, M. F., Fraternale, A., Duranti, A., De Marco, C., Fanelli, M., Zaffaroni, N., Brandi, G. and Magnani, M. 2011. The indole-3-carbinol cyclic tetrameric derivative CTet inhibits cell proliferation via ocerexpression of p21/CDKN1A in both estrogen receptor-positive and triple-negative breast cancer cell lines. Breast Cancer Res. 13(2): R33, doi: 10.1186/bcr2855, 15 pages

258. De Stefani, E., Boffetta, P., Ronco, A. L., Deneo-Pellegrini, H., Acosta, G., Gutierrez, L. P. and Mendilaharsu, M. 2008. Nutrient patterns and risk of lung cancer: A factor analysis in Uruguayan men. Lung cancer. 61(3):283-291

259. De, P., Dey, N., Terakedis, B., Bergsagel, P. L., Li, Z. H., Mahadevan, D., Garlich, J. R., Trudel, S., Makale, M. T. and Durden, D. L. 2013. Anintegrin-targeted, pan-isoform, phosphoinositide-3-kinase inhibitor, SF1126, has activity against multiple myeloma in vivo. Cancer Chemother Pharmacol. 71(4): 867-81

260. Debeb, B. G., Cohen, E. N., Boley, K., Freiter, E. M., Li, L., Robertson, F. M., Reuben, J. M., Cristofanilli, M., Buchholz, T. A. and Woodward, W. A. 2012. Pre-clinical studies of Notch signaling inhibitor RO4929097 in inflammatory breast cancer cells. Breast Cancer Res Treat. 134(2): 495-510

261. Delpire, E. and Lauf, P. K. 1992. Kinetics of DIDS inhibition of swelling-activated K-Cl cotransport in low K sheep erythrocytes. J Membr Biol. 126(1): 89-96, PMID: 1593613

262. Demark-Wahnefried, W., Price, D.T., Polascik, T.J., Robertson, C. N., Anderson, E. E., Paulson, D. F., Walther, P. J., Gannon, M. and Vollmer, R. T. 2001. Pilot study of dietary fat restriction and flaxseed supplementation in men with prostate cancer before surgery. Exploring the effects on hormonal levels, prostate-specific antigen, and histopathologic features. Urology. 58(6 Suppl 1): 42–52.

263. Dembinska-Kiec, A., Polus, A., Kiec-Wilk, B., Grzybowska, J., Mikolajczyk, M., Hartwich, J., Razny, U., Szumilas, K., Banas, A.,

Bodzioch, M., Stachura, J., Dyduch, G., Laidler, P., Zagajewski, J., Langman, T. and Schmitz, G. 2005. Proangiogenic activity of beta-carotene is coupled with the activation of endothelial cell chemotaxis. Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease. 1740(2): 222-239

264. Deng, L., Ding, W. and Granstein, R. D. 2003. Thalidomide inhibits tumor necrosis factor-alpha production and antigen presentation by Langerhans cells. J Invest Dermatol. 121(5): 1060-5

265. Deng, Y. T., Huang, H. C. and Lin, J. K. 2010. Rotenone induces apoptosis in MCF-7 human breast cancer cell-mediated ROS through JNK and p38 signaling. Mol Carcinog. 49(2): 141-51

266. Derosa, G., Matfioli, P., D'Angelo, A., Salvadeo, S., Ferrai, I., Fogari, E., Mereu, R., Randazzo, S. and Cicero, A. 2009. Effects of long chain w-3 fatty acids on metalloproteinases and their inhibitors in combined dyslipidemia patients. Expert opinion on Pharmacotherapy. 10(8): 1239-1247

267. Derr, R. L., Ye, X., Islas, M. U., Desideri, S., Saudek, C. D. and Grossman, S. A. 2009. Association between hyperglycemia and survival in patients with newly diagnosed glioblastoma. J Clin Oncol. 27(7): 1082-1086

268. Deryugina, E.I. and Quigley, J. P. 2006. Matrix metalloproteinases and tumor metastasis. Cancer and Metastasis Reviews. 25(1): 9-34, doi:10.1007/s10555-006-7886-9

269. Deshmukh, V., Hu, H., Barroga, C., Bossard, C., Samumed, K. C., Dellamary, L., Stewart, J., Chiu, K., Ibanez, M., Pedraza, M., Seo, T., Cho, S., Cahiwat, J., Tam, B., Tambiah, J. R. S., Hood, J., Lane, N. E. and Yazıcı, Y. 2018. A small molecule inhibitor of the Wnt pathway for the treatment of osteoarthritis of the knee. Osteoarthritis and Cartilage. 26(1): 18-27, https: // doi.org / 10.1016 / j.joca.2017.08.15

270. Devaraj, S. and Jialal, I. 2005. α-tocopherol decreases tumor necrosis factor-α mRNA and protein from activated human monocytes by inhibition of 5-lipoxygenase. Free Radical Biology and Medicine. 38(9): 1212-1220

271. Devaud, N. and Gallinger, S. 2013. Chemotherapy of MMR-deficient colorectal cancer. Fam Cancer. 12(2):301-6

272. Devi, K. P., Rajavel, T., Habtemariam, S., Nabavi, S. F. and Nabavi, S. M. 2015. Molecular mechanisms underlying anticancer effects of myricetin. Life Sci. 142:19-25, doi:10.1016/j.lfs.2015.10.004

273. DeWeese, T. L., Shipman, J. M., Larrier, N. A., Buckley, N. M., Kidd, L. R., Groopman, J. D., Cutler, R. G., te Riele, H. and Nelson, W. G. 1998. Mouse embryonic stem cells carrying one or two defective Msh2 alleles respond abnormally to oxidative stress inflicted by low-level radiation. Proc Natl Acad USA. 95(20): 11915-20

274. Dhingra, D., Michael, M., Rajput, H. and Patil, R. T. 2012. Dietary fibre in foods: a review. J Food Sci Tchnol. 49(3): 255-266

275. Dhir, A., Padi, S. S., Naidu, P. S. and Kulkarni, S. K. 2006. Protective effect of naproxen (non-selective COX-inhibitor) or rofecoxib (selective COX-2 inhibitor) on immobilization stress-induced behavioral and biochemical alterations in mice. Eur J Pharmacol. 535(1-3): 192-8

276. Dickinson, D., Yu, H., Ohno, S., Thomas, C., DeRossi, S., Ma, Y., Yates, N., Hahn, E., Bisch, F., Yamamoto, T. and Hsu, S. 2014. Epigallocatechin-3-gallate prevents autoimmune-associated down-regulation of p21 in salivary gland cells through a p53-independent pathway. Inflamm Allergy Drug Targets. 13(1): 15-24, PMID: 24329914

277. Dickinson, S. E., Melton, F. T., Olson, E. R., Zhang, J., Saboda, K. and Bowden, G. T. 2009. Inhibition of AP-1 by sulforaphane involves interaction with cysteine in the cFos DNA-binding domain; implications for chemoprevention of UVB-induced skin cancer. Cancer Res. 69(17): 7103-7110

278. Dickson, B. C., Mulligan, A. M., Zhang, H., Lockwood, G., O'Malley, F. P., Egan, S. E. and Reedijk, M. 2007. High-level JAG1mRNA and protein predict poor outcome in breast cancer. Mod Pathol. 20(6): 685-93

279. Diez-Juan, A. and Andres, V. 2001. The growth suppressor p27 (Kip1) protects against diet-induced atherosclerosis. FASEB J. 15(11): 1989-95

280. Dinarello, C. A. 2010. Why not treat human cancer with interleukin-1 blockade?. Cancer Metastasis Rev. 29(2): 317-329
281. Ding, N., Bonham, E. M., Hannon, B. E., Amick, T. R., Baylin, S. B. and O'Hagan, H. M. 2016. Mismatch repair proteins recruit DNA methyltransferase 1 to sites of oxidative DNA damage. J Mol Cell Biol. 8(3): 244-54
282. Diskin, S. J., Capasso, M., Schnepp, R. W., Cole, K. A., Attiyeh, E. F., Hou, C., Diamond, M., Carpenter, E. L., Winter, C., Lee, H., Jagannathan, J., Latorre, V., Iolascon, A., Hakonarson, H., Devoto, M. and Maris, J. M. 2012. Common variation at 6q16 within HACE1 and LIN28B influences susceptibility to neuroblastoma. Nat Genet. 44(10): 1126-30
283. Dixit, D., Ghildiyal, R., Anto, N. P., Ghosh, S., Sharma, V. and Sen, E. 2013. Guggulsterone sensitizes glioblastoma cells to Sonic hedgehog inhibitor SANT-1 induced apoptosis in a Ras/ NFkB dependent manner. Cancer Letters. 336(2): 347-358
284. Do, M. H., Lee, S. S., Jung, P. J. and Lee, M. H. 2003. Intake of dietary fat and vitamin in relation to breast cancer risk in Korean women. J Korean Med Sci. 18(4): 534-40
285. Do, M. T., Kim, H. G., Khanal, T., Choi, J. H., Kim, D. H., Jeong, T. C. and Jeong, H. G. 2013. Metformin inhibits heme oxygenase-1 expression in cancer cells through inactivation of Raf-ERK-Nrf2 signaling and AMPK-independent pathways. Toxicology and Applied Pharmacology. 271(2): 229-238
286. Dolcet, X., Llobet, D., Pallares, J. and Matias-Guiu, X. 2005. NF-kB in development and progression of human cancer. Virchows Arch. 446: 475-482, doi:10.1007/S00428-005-1264-9
287. Don-Doncow, N., Escobar, Z., Johansson, M., Kjellstrom, S., Garcia, V., Munoz, E., Sterner, O., Bjartell, A. and Hellsten, R. 2014. Galliellactone is a direct inhibitor of the transcription factor STAT3 in prostate cancer cells. J Biol Chem. 289(23): 15969-78
288. Donnini, S., Finetti, F., Lusini, L., Morbidelli, L., Cheynier, V., Barron, D., Williamson, G., Waltenberger, J. and Ziche, M. 2006. Divergent affects of quercetin conjugates on angiogenesis. Br J Nutr. 95(5): 1016-23

289. Duan, J., Yue, W., JianYu, E., Malhotra, J., Lu, S., Gu, J., Xu, F. and Tan, X. 2016. In vitro comparative studies of resveratrol and triacetylresveratrol on cell proliferation, apoptosis, and STAT3 and NFkB signaling in pancreatic cancer cells. Scientific Reports. 6:31672, doi:10.1038/srep31672

290. Duan, Z., Bradner, J., Greenberg, E., Mazitschek, R., Foster, R., Mahoney, J. and Seiden, M. V. 2007. 8-benzyl-4-oxo-8-azabicyclo[3.2.1]oct-2-ene-6,7-dicarboxylic acid (SD-1008), a novel janus kinase 2 inhibitor, increases chemotherapy sensitivity in human ovarian cancer cells. Mol Pharmacol. 72(5): 1137-45

291. Dudzik, P., Dulinska-Litewka, J., Wyszko, E., Jedrychowska, P., Opalka, M., Barciszewski, J. and Laidler, P. 2011. Effects of kinetin riboside on proliferation and proapoptotic activities in human normal and cancer cell lines. J Cell Biochem. 112(8): 2115-24

292. Duffy, P. J., Harrington, M. E., Salituro, G. F., Cochran, E. J., Green, J., Gao, H., Bemis, W. G., Evindar, G., Galullo, P. V., Ford, J. P., Germann, A. U., Wilson, P. K., Bellon, F. S., Chen, G., Taslimi, P., Jones, P., Huang, C., Pazhanisamy, S., Wang, Y., Murcko, A. M. and Michael, S. S. 2011. The discovery of VX-745: A novel and selective p38α kinase inhibitor. ACS Med Chem Lett. 2 (10): 758-763

293. Dufies, M., Giuliano, S., Ambrosetti, D., Claren, A., Ndiaye, P. D., Mastri, M., Moghrabi, W., Cooley, L. S., Ettaiche, M., Chamorey, E., Parola, J., Vial, V., Lupu-Plesu, M., Bernhard, J. C., Ravaud, A., Borchiellini, D., Ferrero, J. M., Bikfalvi, A., Ebos, J. M., Khabar, K. S., Grepin, R. and Pages, G. 2017. Sunitinib stimulates expression of VEGFC by tumor cells and promotes lymphangiogenesis in clear renal cell carcinomas. Cancer Res. 77(5):1212-1226

294. Dumble, M., Crouthamel, M., Zhang, S., Schaber, M., Levy, D., Robell, K., Liu, Q., Figueroa, D. J., Minthorn, E. A., Seefeld, M. A., Rouse, M. B., Rabindran, S. K., Heerding, D. A. and Kumar, R. 2014. Discovery of novel AKT inhibitors with enhanced anti-tumor effects in combination with the MEK inhibitor. PlosOne. 9(6): e100880, doi: 10.1371/journal.pone.0100880, 11 pages

295. Durazzo, A., Zaccaria, M., Polito, A., Maiani, G. and Carcea, M. 2013. Lignan content in cereals, buckwheat and derived foods. Foods. 2(1): 53-63, doi: 10.3390/foods2010053
296. Dutto, I., Sukhanova, M., Tilhon, M., Cazzalini, O., Stivala, A. L., Scovassi, I. A., Lavrik, O. and Prosperi, E. 2016. P21CDKN1A regulates the binding of Poly(ADP-Ribose) polymerase-1 to DNA repair intermediates. Plos One. 11(1): e0146031, 15 pages
297. Eales, K. L., Hollinshead, K. E. R. and Tennant, D. A. 2016. Hypoxia and metabolic adaptation of cancer cells. Oncogenesis. 5:e190, doi:10.1038/oncsis.2015.50, 8 pages
298. Edgar, A. K., Nannini, M., Hong, R., Eigenbrot, C., Schmidt, S., Young, A., Sampath, D., Wallin, J. J. and Friedman, S. L. 2015. Abstract 2672: Characterization of the enhanced potency of PI3K inhibitor taselinib (GDC-0032) in PI3K mutant cell lines and models. Cancer Res. 75: 2672, doi: 10.1158/1538-7445. AM2015-2672
299. EFSA Panel on Contaminants in the Food Chain (CONTAM). 2016. Acute health risks related to the presence of cyanogenic glycosides in raw apricot kernels and products derived from raw apricot kernels. EFSA Journal. 14(4): 4424, doi: 10. 2903 / j. efsa. 2016. 4424, 47 pages
300. Egner, A. P., Chen, G. J., Wang, B. J., Wu, Y., Sun, Y., Lu, H. J., Zhu, J., Zhang, H. Y., Chen, S. Y., Friesen, M. D., Jacobson, P. L., Munoz, A., Ng, D., Qian, G. S., Zhu, R. Y., Chen, Y. T., Botting, N. P., Zhang, Q., Fahey, W. J., Talalay, P., Groopman, D. J. and Kensler, W. T. 2011. Bioavailability of sulforaphane from two broccoli sprout beverages: Results of a short-term, cross-over clinical trial in Qidong, China. Cancer Prev Res. 4(3): 384-395
301. Ehrhardt, M., Craveiro, B. R., Holst, I. M., Pietsch, T. and Dilloo, D. 2015. The PI3K inhibitor GDC-0941 displays promising in vitro and in vivo efficacy for targeted medulloblastoma therapy. Oncotarget. 6(2): 802-813
302. Eichholzer, M., Stahelin, H. B., Gutzwiller, F., Lüdin, E. and Bernasconi, F. 2000. Association of low plasma cholesterol with mortality for cancer at various sites in men:17-y follow-up of the prospective Basel study. Am J Clin Nutr. 71(2):569-574

303. Eide, M. J., Johnson, D. A., Jacobsen, G. R., Krajenta, R. J. Rao, S., Lim, H. W. and Johnson, C. C. 2011. Vitamin D and nonmelanoma skin cancer in a health maintenance organization cohort. Arch Dermatol. 147(12):1379-1384

304. Ekoff, M., Kaufmann, T., Engström, M., Motoyama, N., Villunger, A., Jönsson, J., Strasser, A. and Nilsson, G. 2007. The BH3-only protein PUMA plays an essential role in cytokine deprivation-induced apoptosis of mast cells. Blood. 110(9): 3209-3217

305. Elbekai, R. H., Duke, J. and El-kadi, O. S. A. 2007. Ascorbic acid differentially modulates the induction of heme oxygenase-1, NAD(P)H: quinine oxidoreductase 1 and glutathione S-transferase Ya by As^{3+}, Cd^{2+} and Cr^{6+}. Cancer Letters. 246 (1-2): 54-62

306. Elferink, J. G. and de Koster, B. M. 2000. Inhibition of interleukin-8-activated human neutrophil chemotaxis by thapsigargin in a calcium-and cyclic AMP-dependent way. Biochem Pharmacol. 59(4): 369-75

307. Eliassen, H. A., Liao, X., Rosner, B., Tamimi, M. R., Tworoger, S. S. and Hankinson, E. S. 2015. Plasma carotenoids and risk of breast cancer over 20 y of follow-up. Am J Clin Nutr. 101(6):1197-205

308. Ellison, L. F. 2000. Tea and other beverage consumption and prostate cancer risk: a Canadian retrospective cohort study. Eur J Cancer Prev. 9(2): 125-30

309. El-Najjar, N., Chatila, M., Moukadem, H., Vuorela, H., Ocker, M., Gandesiri, M., Schneider-Stock, R. and Gali-Muhtasib, H. 2010. Reactive oxygen species mediate thymoquinon-induced apoptosis and activate ERK and JNK signaling. Apoptosis. 15(2): 183-95

310. Emami, H., Vucic, E., Subramanian, S., Abdelbaky, A., Fayad, A. Z., Du, S., Roth, E., Ballantyne, M. C., Mohler, R. E., Farkouh, E. M., Kim, J., Farmer, M., Li, L., Ehlgen, A., Langenickel, H. T., Velasquez, L., Hayes, W. and Tawakol, A. 2015. The effect of BMS-582949, a p38 mitogen-activated protein kinase (p38 MAPK) inhibitor on arterial inflammation: A multicenter FDG-PET trial. Atherosclerosis. 240(2): 490-496

311. Eom, H. J. and Choi, J. 2010. P38 MAPK activation, DNA damage, cell cycle arrest and apoptosis as mechanisms of toxicity of silver nanoparticles in Jurkat T cells. Environ Sci Technol. 44(21): 8337-42
312. Evangelista, M., Tian, H. and de Sauvage, F. J. 2006. The Hedgehog signaling pathway in cancer. Clin Cancer Res. 12(20pt 1): 5924-8
313. Evangelisti, C., Ricci, F., Tazzari, P., Chiarini, F., Battistelli, M., Falcieri, E., Ognibene, A., Pagliaro, P., Cocco, L., McCubrey, J. A. and Martelli, A. M. 2011. Preclinical testing of the Akt inhibitor triciribine in T-cell acute lymphoblastic leukemia. J Cell Physiol. 226(3): 822-31
314. Evans, A. H., Pancholi, S., Farmer, I., Tornhill, A., Evans, D. B., Johnston, S. R., Dowsett, M. and Martin, L-A. 2010. Egfr/Her2 inhibitor AEE788 increases ER-mediated transcription in Her2/ ER-positive breast cancer cells but functions synergistically with endocrine therapy. Br J Cancer. 102(8): 1235-1243
315. Fabre, N., Rustan, I., de Hoffmann, E. and Quetin-Leclercq, J. 2001. Determination of flavones, flavonol, and flavanone agylycones by negative ion liquid chromatography. American Society for Mass Spectrometry. 12: 707-715, p1151044-0305(01)00226-4
316. Fadaka, A., Ajiboye, B., Ojo, O., Adewale, O., Olayide, I. and Emuowhochere, R. 2017. Biology of glucose metabolization in cancer cells. Journal of Oncological Sciences. 3(2): 45-51
317. Fahey, J. W. and Kensler, T. W. 2007. Role of dietary supplements/ nutraceuticals in chemoprevention through induction of cytoprotective enzymes. Chem Res Toxicol. 20(4): 572-6
318. Fahey, J. W., Stephenson, K. K., Dinkova-Kostova, A. T., Egner, P. A., Kensler, T. W. and Talalay, P. 2005. Chlorophyll, chlorophyllin and related tetrapyrroles are significant inducers of mammalian phase 2 cytoprotective genes. Carcinogenesis. 26(7): 1247-55
319. Fahlbush, F. B., Ruebner, M., Huebner, H., Volkert, G., Bartunik, H., Winterfeld, I., Hartner, A., Menendez-Castro, C., Noegel, S. C., Marek, I., Wachter, D., Schneider-Stock, R., Beckmann,

M. W., Kehl, S. and Rascher, W. 2015. Trophoblast expression dynamics of the tumor suppressor gene gastrokine 2. Histochem Cell Biol. 144(3): 281-91

320. Falk, R., Falk, A., Dyson, M. R., Melidoni, A. N., Parthiban, K., Young, J. L., Roake, W. and McCafferty, J. 2012. Generation of anti-Notch antibodies and their application in blocking Notch signaling in neural stem cells. Methods. 58(1): 69-78, doi: 10.1016/j.ymeth.2012.07.008

321. Fang, D. D., Zhang, C. C., Gu, Y., Jani, J. P., Cao, J., Tsaparikos, K., Yuan, J., Thiel, M., Jackson-Fisher, A., Zong, Q., Lappin, P. B., Hayashi, T., Schwab, R. B., Wong, A., John-Baptiste, A., Bagrodia, S., Los, G., Bender, S., Christensen, J. and VanArsdale, T. 2013. Antitumor efficacy of the dual PI3K/ mTOR inhibitor PF-04691502 in a human xenograft tumor model derived from colorectal cancer stem cells harboring a PIK3CA mutation. PlosOne. 8(6): e67258, doi: 10.1371 / journal. pone. 0067258, 12 pages

322. Fang, J., Xia, C., Cao, Z., Zheng, J. Z., Reed, E. and Jiang, B. H. 2005. Apigenin inhibits VEGF and HIF-1 expression via PI3K/AKT/p70S6K1 and HDM2/p53 pathways. FASEB J. 19(3): 342-53

323. Farabegoli, F., Papi, A., Bartolini, G., Oston, R. and Orlandi, M. 2010. (-)-Epigallocatechin-3-gallate downregulates Pg-P and BCRP in a tamoxifen resistant MCF-7 cell line. Phytomedicine. 17(5): 356-362

324. Farhat, F. S. and Houhou, W. 2013. Targeted therapies in non-small cell lung carcinoma: what have we achieved so far?. Ther Adv Med Oncol. 5(4): 249-270

325. Farmaki, E., Chatzistamou, I., Kaza, V. and Kiaris, H. 2016. A CCL8 gradient drives breast cancer cell dissemination. Oncogene. 35(49): 6309-6318

326. Fasano, E., Serini, S., Piccioni, E., Toesca, A., Monego, G., Cittadini, R. A., Ranelletti, O. F. and Calviello, G. 2012. DHA induces apoptosis by altering the expression and cellular location of GRP78 in colon cancer cell lines. Biochimica et Biophysica Acta (BDA)-Molecular Basis of Disease. 1822(11):1762-1772

327. Fatima, I., El-Ayachi, I., Taotao, L., Lillo, M. A., Krutilina, R., Seagroves, T. N., Radaszkiewicz, T. W., Hutnan, M., Bryja, V., Krum, S. A., Rivas, F. and Miranda-Carboni, A. G. 2017. The natural compound *Jatrophone* interferes with Wnt/β-catenin signaling and inhibits proliferation and EMT in human triple-negative breast cancer. PlosOne. 12(12): e0189864, doi: 10.1371/journal.pone.0189864, 18 pages

328. Favia, A., Desideri, M., Gambara, G., D'Alessio, A., Ruas, M., Esposito, B., Del Bufalo, D., Parrington, J., Ziparo, E., Palombi, F., Galione, A. and Filippini, A. 2014. VEGF-induced neoangiogenesis is mediated by NAADP and two-pore channel-2-dependent Ca2+ signaling. Proc Natl Acad Sci USA. 111(44): E4706-E4715

329. Fedirko, V., Bostick, R. M., Flanders, W. D., Long, Q., Shaukat, A., Rutherford, R. E., Daniel, C. R., Cohen, V. and Dash, C. 2009. Effects of vitamin D and calcium supplementation on markers of apoptosis in normal colon mucosa: a randomized, double-blind, placebo-controlled clinical trial. Cancer Prev Res. (Phila). 2(3): 213-223

330. Feldman, R. I., Wu, J. M., Polokoff, M. A., Kochanny, M. J., Dinter, H., Zhu, D., Biroc, S. L., Alicke, B., Bryant, J., Yuan, S., Buckman, B. O., Lentz, D., Ferrer, M., Whitlow, M., Adler, M., Finster, S., Chang, Z. and Arnaiz, D. O. 2005. Novel small molecule inhibitors of 3-phosphoinositide-dependent kinase-1. J Biol Chem. 280(20): 19867-74

331. Femenia, A., Rossello, C., Mulet, A. and Canellas, J. 1995. Chemical composition of bitter and sweet apricot kernels. Journal of Agricultural and Food Chemistry. 43(2): 356-361

332. Fernandez de Mattos, S., Essafi, A., Soeiro, I., Pietersen, A. M., Birkenkamp, K. U., Edwards, C. S., Martino, A., Nelson, B. H., Francis, J. M., Jones, M. C., Brosens, J. J., Coffer, P. J. and Lam, E. W. 2004. FOXO3a and BCR-ABL regulate cyclin D2 transcription through a STAT5/BCL6-dependent mechanism. Mol Cel Biol. 24(22): 10058-71

333. Fiaschetti, G., Grotzer, M. A., Shalaby, T., Castelletti, D. and Arcaro, A. 2011. Quassinoids: From traditional drugs to new

cancer therapeutics. Current Medicinal Chemistry. 18(3): 316-328

334. Fiedler, U., Cornelius, A., Akawardhani, S., Dawson, K. M., Gilboy, P., Stumpp, M. T., Dolado, I. and Molecular Partners, AG. 2014. Potency of bortezomib in combination with MPO250, a bispecific VEGF-and HGF-targeting darpin, in a preclinical multiple myeloma model. 2014 ASCO Annual Meeting. J Clin Oncol. 32, Suppl; Abstract: e19574

335. Filipovic, A., Lombardo, Y., Fronato, M., Abrahams, J., Aboagye, E. Nguyen, Q., d'Aqua, B. B., Ridley, A., Green, A., Rahka, E., Ellis, I., Recchi, C., Przulj, N., Sarajlic, A., Alattia, J., Fraering, P., Deonarain, M. and Coombes, R. C. 2014. Anti-nicastrin monoclonal antibodies elicit pleiotropic anti-tumour pharmacological effects in invasive breast cancer cells. Breast Cancer Res Treat. 148(2): 455-462

336. Flores, K., Yadav, S. S., Katz, A. A. and Seger, R. 2019. The nuclear translocation of mitogen-activated protein kinases: Molecular mechanisms and use as novel therapeutic target. Neuroendocrinology. 108(2): 121-131

337. Fluteau, A., Ince, P. G., Minett, T., Matthews, F. E., Brayne, C., Garwood, C. J., Ratcliffe, L. E., Morgan, S., Heath, P. R., Shaw, P. J., Wharton, S. B., Simpson, J. E. and MRC Cognitive Function Ageing Neuropathology Study Group. 2015. Neuroscience Letters. 609: 11-17, http://dx.doi.org/ 10.1016/ s.neulet.2015.10.001

338. Folsom, A. R. and and Demissie, Z. 2004. Fish Intake, Marine Omega-3 Fatty Acids, and Mortality in a Cohort of Postmenopausal Women. American Journal of Epidemiology.160(10): 1005-1010

339. Fonseca, L. C., Dadarkar, S. S., Lobo, A. S., Suthar, A. C., Chauhan, V. S., Chandrababu, S., Sharma, S. D., Dagia, N. M. and Padigaru, M. 2010. 7-hydroxyfrullanolide, a sesquiterpene lactone, inhibits pro-inflammatory cytokine production from immune cells and is orally efficacious in animal models of inflammation. European Journal of Pharmacology. 644 (Issues 1-3): 220-229, https://doi.org/10.1016/j.ejphar.2010.06.052

340. Foster, P., Yamaguchi, K., Hsu, P. P., Qian, F., Du, X., Wu, J., Won, K. A., Yu, P., Jaeger, C. T., Zhang, W., Marlowe, C. K., Keast, P., Abulafia, W., Chen, J., Young, J., Plonowski, A., Yakes, F. M., Chu, F., Engell, K., Bentzien, F., Lam, S. T., Dale, S., Yturralde, O., Matthews, D. J., Lamb, P. and Laird, A. D. 2015. The selective PI3K inhibitor XL147 (SAR245408) inhibits tumor growth and survival and potentiates the activity of chemotherapeutic agents in preclinical tumor models. Mol Cancer Ther. 14(4): 931-40

341. Francis, R. E., Myatt, S. S., Krol, J., Hartman, J., Peck, B., McGovern, U. B., Wang, J., Guest, S. K., Filipovic, A., Gojis, O., Palmieri, C., Peston, D., Shousha, S., Yu, Q., Sicinski, P., Coombes, R. C. and Lam, E. W. 2009. FoxM1 is a downstream target and marker of HER2 overexpression in breast cancer. Int J Oncol. 35(1): 57-68 PMID: 19513552

342. Franco, R., Onatibia-Astibia, A. and Martinez-Pinilla, E. 2013. Health benefits of methylxanthines in cacao and chocolate. Nutrients. 5(10): 4159-4173

343. Fraser, G. E., Beeson, W. L. and Phillips, R. L. 1991. Diet and lung cancer in California seventh-day adventists. Am J Epidemiol. 133(7): 683-93

344. Friedman, J. A., Wise, S. C., Hu, M., Gouveia, C., Broek, R. V., Freudlsperger, C., Kannabiran, V. R., Arun, P., Mitchell, J. B., Chen, Z. and Van Waes, C. 2013. HSP90 inhibitor SNX5422/2112 targets the dysregulated signal and transcription factor network and malignant phenoyype of head and neck squamous cell carcinoma. Translational Oncology. 6(4): 429-441

345. Friedmann, Y., Shriki, A., Bennett, R. E., Golos, S., Diskin, R., Marbach, I., Bengal, E. and Engelberg, D. 2006. JX401, a p38α inhibitor containing a 4-benzylpiperidine motif, identified via a novel screening system in yeast. Molecular Pharmacology. 70(4): 1395-1405

346. Fritsch, C., Huang, A., Chatenay-Rivauday, C., Schbell, C., Reddy, A., Liu, M., Kauffmann, A., Guthy, D., Erdmann, D., De Pover, A., Furet, P., Gao, H., Ferretti, S., Wang, Y., Trappe, J., Brachmann, S. M., Maira, S. M., Wilson, C., Boehm, M.,

Garcia-Echeverria, C., Chene, P., Wiesmann, M., Cozens, R., Lehar, J., Schlegel, R., Caravatti, G., Hoffman, F. and Sellers, W. R. 2014. Characterization of the novel and specific PI3Kα inhibitor NVP-BYL719 and development of the patient stratification strategy for clinical trials. Mol Cancer Ther. 13(5): 1117-29

347. Fu, L., Peng, J., Zhao, S., Zhang, Y., Su, X. and Wang, Y. 2017. Lactic acid bacteria-specific induction of $CD4^{+}TFoxp3^{+}T$ cells ameliorates shrimp tropomyosin-induced allergic response in mice via suppression of mTOR signaling. Scientific Reports. 7: 1987, doi: 10.1038/s41598-017-02260-8, 14 pages

348. Fu, Y., O'Connor, M. L., Shepherd, G. T. and Nachtigal, W. M. 2003. The p38 MAPK inhibitor, PD169316, inhibits transforming growth factor β-induced Smad signaling in human ovarian cancer cells. Biochemical and Biophysical Research Communications. 310(2): 391-397

349. Fu, Y., Zheng, J., Yang, B. and Li, D. 2015. Effect of individual Omega-3 fatty acids on the risk of prostate cancer: A systematic review and dose-response meta-analysis of prospective cohort studies. J Epidemiol. 25(4): 261-274

350. Fujioka, N., Fritz, V., Upadhyaya, P., Kassie, F. and Hecht, S. S. 2016. Research on cruciferous vegetables, indole-3-carbinol, and cancer prevention: A tribute to Lee W. Wattenberg. Mol Nutr Food Res. 60: 1228-1238, doi: 10.1002/mnfr.201500889

351. Fujiwara, T., Kanazawa, S., Ichibori, R., Tanigawa, T., Magome, T., Shingaki, K., Miyata, S., Tohyama, M. and Hosokawa, K. 2014. L-arginine stimulates fibroblast proliferation through the GPRC6A-ERK1/2 and PI3K/Akt pathway. PlosOne. 9(3): e921168, doi:10.1371/journal.pone.0092168, 9 pages

352. Fukuda, H., Ohashi, R., Ohashi, N. and Yabuuchi, H. 2010. Estimation of transporters involved in the hepatobiliary transport of TAO201CA using sandwich-cultured rat hepatocytes from normal and multidrug reistance-associated protein 2 deficient rats. Drug Metabolism and Deposition: the biological fate of chemicals. Drug Metabol Dispos. 38(9): 1505-1513

353. Fukui, M., Kang, K. S., Okada, K. and Zhu, B. T. 2013. EPA, an omega-3 fatty acid, induces apoptosis in human pancreatic cancer cells: role of ROS accumulation, caspase-8 activation, and autophagy induction. J Cell Biochem. 114(1): 192-203

354. Fukushima, N., Minami, Y., Hayakawa, F., Kiyoi, H., Sadarangi, A., Jamieson, C. HM. and Naoe, T. 2013. Treatment with Hedgehog inhibitor, PF-04449913, attenuates leukemia-initiation potential in acute myeloid leukemia cells. Blood. 122:21, 2 pages, Accession number: 000331385003286

355. Fumo, G., Akin, C., Metcalfe, D. D. and Neckers, L. 2004. 17-allylamino-17-demethoxygeldanamycin (17-AAG) is effective in down-regulating mutated, constitutively activated KIT protein in human mast cells. 103(3): 1078-1084

356. Gaggar, A., Hector, A., Bratcher, P. E., Mall, M. A., Griese, M. and Hartl, D. 2011. Series 'Matrix metalloproteinases in lung health and disease'. Eur Respir J. 38(2): 721-727

357. Gagliardi, A. R., Hennig, B. and Collins, D. C. 1996. Antiestrogens inhibit endothelial cell growth stimulated by angiogenic growth factors. Anticancer Res. 16(3A): 1101-6

358. Galanis, J. D., Kolonel, N. L., Lee, J. and Nomura, A. 1998. Intakes of selected foods and beverages and the incidence of gastric cancer among the Japanese residents of Hawaii: a prospective study. International Journal of Epidemiology. 27(2): 173-180

359. Gallily, R., Breuer, A. and Mechoulam, R. 2000. 2-Arachidonylglycerol, an endogenous cannabinoid, inhibits tumor necrosis factor-alpha production in murine macrophages, and in mice. Eur J Pharmacol. 406(1): R5-7i https://doi.org/10.1016/S0014-2999(00)00653-1

360. Galluzzi, L., De Santi, M., Crinelli, R., De Marco, C., Zaffaroni, N., Duranti, A., Brandi, G. and Magnani, M. 2012. Induction of endoplasmic reticulum stress response by the indole-3-carbinol cyclic tetrameric derivative CTet in human breast cancer cell lines. Plos One. 7(8): e43249, doi: 10.1371/journal.pone.0043249, 14 pages.

361. Galustian, C., Meyer, B., Labarthe, M. C., Dredge, K., Klaschka, D., Henry, J., Todryk, S., Chen, R., Muller, G., Stirling, D., Schafer, P., Bartlett, J. B. and Dalgleish, A. G. 2009. The anti-cancer agents lenalidomide and pomalidomide inhibit the proliferation and function of T regulatory cells. Cancer Immunol Immunother. 58(7): 1033-45

362. Ganai, A. A., Khan, A. A., Malik, A. Z. and Farooqi, H. 2015. Genistein modulates the expression of NF-kB and MAPK (p-38 and ERK1/2), thereby attenuating D-galactosamine induced fulminant hepatic failure in Wistar rats. Toxicology and Applied Pharmacology. 283(2): 139-146

363. Gandhi, J., Gaur, N., Khera, L., Kaul, R. and Robertson, E. S. 2015. COX-2 induces lytic reactivation of EBV through PGE2 by modulating the EP receptor signaling pathway. Virology. 484: 1-14, doi: 10.1016/j.virol.2015.05.006

364. Gann, P. H., Ma, J., Giovannucci, E., Willett, W., Sacks, F. M., Hennekens, C. H. and Stampfer, M. J. 1999. Lower prostate cancer risk in men with elevated plasma lycopene levels: results of a prospective analysis. Cancer Res. 59(6): 1225-30

365. Gao, A., Ke, Z., Wang, J., Yang, J., Chen, S. and Chen, H. 2013. Apigenin sensitizes doxorubicin-resistant hepatocellular carcinoma BEL-7402/ADM cells to doxorubicin via inhibiting PI3K/Akt/Nrf2 pathway. Carcinogenesis. 34(8): 1806-1814

366. Gao, Q., Yuan, Y., Gan, H. and Peng, Q. 2015. Resveratrol inhibits the hedgehog signaling pathway and epithelial-mesenchymal transition and suppresses gastric cancer invasion and metastasis. Oncology Letters. 9(5): 2381-2387

367. Garbe, C., Krasagakis, K., Zouboulis, C. C., Schröder, K., Krüger, S., Stadler, R. and Orfanos, C. E. 1990. Antitumor activities of interferon alpha, beta, and gamma and their combinations on human melanoma cells in vitro: changes of proliferation, melanin synthesis, and immunophenotype. J Invest Dermatol. 95(6Suppl): 231S-237S

368. Garcia, C., Bartsch, D. U., Rivero, M. E., Hagedorn, M., McDermott, C. D., Bergeron-Lynn, G., Cheng, L., Appelt, K. and Freeman, W. R. 2002. Efficacy of prinomastat (AG3340),

a matrix metalloprotease inhibitor, in treatment of retinal neurovascularization. Curr Eye Res. 24(1): 33-8 PMID:12187492

369. Garcia, V. P., Rocha, H. N. M., Silva, G. M., Amaral, T. A. G., Secher, N. H., Nabrega, A. C. L., Vianna, L. C. and Rocha, N. G. 2016. Exogenous L-arginine reduces matrix-metalloproteinase-2 and -9 activities and oxidative stress in patients with hypertension. Life Sciences. 157:125-130, https: // doi.org/10.1016/j.lfs.2016.06.006

370. Garcia-Bennett, A. E., Xiao, C., Zhou, C., Castle, T., Miyasaka, K. and Terasaki, O. 2011. Bicontinuous cubic mesoporous materials with biphasic structures. Chemistry. 17(48): 13510-6

371. Garlich, J. R., De, P., Dey, N., Su, J. D., Peng, X., Miller, A., Murali, R., Lu, Y., Mills, G. B., Kundra, V., Miller, A., Murali, R., Lu, Y., Mills, G. B., Kundra, V., Shu, H. K., Peng, Q. and Durden, D. L. 2008. A vascular targeted pan phosphoinositide 3-kinase inhibitor prodrug, SF1126, with antitumor and antiangiogenic activity. Cancer Res. 68(1): 206-15

372. Gatenby, A. R. and Gillies, J. R. 2005. Why do cancers have high aerobic glycolysis?. Nature Reviews Cancer. 4: 891-899, doi: 10.1038/nrc1478

373. Gates, A. M., Tworoger, S. S., Hecht, L. J., De Vivo, I., Rosner, B. and Hankinson, S. E. 2007. A prospective study of dietary flavonoid intake and incidence of epithelial ovarian cancer. International of Cancer. 121(10): 2225-2232

374. Gates, A. M., Vitonis, F. A., Tworoger, S. S., Rosner, B., Titus-Ernstoff, L., Hankinson, E. S. and Cramer, W. D. 2009. Flavonoid intake and ovarian cancer risk in a population-based case-control study. Int J Cancer. 124(8): 1918-1925

375. Gato, Y., Kurozumi, A., Nohata, N., Kojima, S., Matsushita, R., Yoshino, H., Yamazaki, K., Ishida, Y., Ichikawa, T., Naya, Y. and Seki, N. 2016. The microRNA signature of patients with sunitinib failure: regulation of UHRF1 pathways by microRNA-101 in renal cell carcinoma. Oncotarget. 7(37): 59070-59086

376. Gavalas, N. G., Tsiatas, M., Tsitsilonis, O., Politi, E., Ioannou, K., Ziogas, A. C., Rodolakis, A., Vlahos, G., Thomakos, N.,

Haidopoulos, D., Terpos, E., Antsaklis, A., Dimopoulos, M. A. and Bamias, A. 2012. VEGF directly suppresses activation of T cells from ascites secondary to ovarian cancer via VEGF receptor type 2. Br J Cancer. 107(11): 1869-1875

377. Gavia, M.H., Couto, R.C., Oyama, L.M. et al. 2003. Diets rich in polyunsaturated fatty acids effect on hepatic metabolism in rats. Nutrition. 19(2): 144–149.

378. Geelen, A., Schouten, J.M., Kamphuis, C. *et al.* 2007. Fish consumption, n-3 fatty acids and colorectal cancer: a meta-analysis of prospective cohort studies. American Journal of Epidemiology. 116*(10)*: 1116–1125.

379. Geiger, K., Hagenbuchner, J., Rupp, M., Fiegl, H., Sergi, C., Meister, B., Kiechl-Kohlendorfer, U., Müller, T., Ausserlechner, M.J. and Obexer, P. 2012. FOXO3/FKHRL1 is activated by 5-aza-2-deoxycytidine and induces silenced caspase-8 in neuroblastoma. Mol. Biol. Cell. 23(11):2226-2234

380. Geiger, R., Rieckmann; J. C., Wolf, T., Basso, C., Feng, Y., Fuhrer, T., Kodadeeva, M., Picotti, P., Meissner, F., Mann, M., Zamboni, N., Sallusto, F. and Lanzavecchia, A. 2016. L-Arginine modulates T cell metabolism and enhances survival and anti-tumor activity. Cell. 167(3): 829-842.e13, doi: 10.16/j. cell2016.09.031

381. Geng, Y., Michowski, W., Chick, M. J., Wang, E. Y., Jecrois, M. E., Sweeney, E. K., Liu, L., Han, R. C., Ke, N., Zagozdzon, A., Sicinski, E., Bronson, T. R., Gygi, P. S. and Sicinski, P. 2018. Kinase-independent function of E-type cyclins in liver cancer. PNAS. https: // doi.org / 10.1073 / pnas. 1711477115, 6 pages

382. Gerhauser, C., Klimo, K., Heiss, E., Neumann, I., Gamal-Eldeen, A., Knauft, J., Liu, G. Y., Sitthimonchai, S. and Frank, N. 2003. Mechanism-based in vitro screening of potential cancer chemopreventive agents. Mutant Res. 523-524:163-172, https://doi.org/10.1016/S0027-5107(02)00332-9

383. Geuna, E., Milani, A., Martinello, R., Aversa, C., Valabrega, G., Scabtriti, M. and Montemurro, F. 2015. Buparlisib, an oral pan-PI3K inhibitor for the treatment of breast cancer. Expert Opin Investig Drugs. 24(3): 421-31

384. Gialeli, C., Theocharis, A. D. and Karamanos, N. K. 2011. Roles of matrix metalloproteinases in cancer progression and their pharmacological targeting. FEBS. 278(1): 16-27 doi: 10.1111/j.1742-4658.2010.07919.x

385. Gill, K. J., Franke, A. A., Morris, S. J., Cooney, V. R., Wilkens, R. L., Le Marchand, L., Goodman, T. M., Henderson, E. B. and Kolonel, N. L. 2009. Association of selenium, tocopherols, carotenoids, retinol, and 15-isoprostane F2t in serum or urine with prostate cancer risk. The multiethnic cohort. Cancer Causes Control. 20(7): 1161-1171

386. Gills, J. J. and Dennis, P. A. 2009. Perifosine: update on a novel Akt inhibitor. Curr Oncol Rep. 11(2): 102-110

387. Giovannucci, E., Rimm, B. E., Liu, Y., Stampfer, J. M. and Willett, C. W. 2002. A prostective study of tomato products, lycopene, and prostate cancer risk. Journal of the National Cancer Institute. 94(5): 391-398

388. Giovannucci, E., Stampfer, M. J., Colditz, G. A., Hunter, D. J., Fuchs, C., Rosner, B. A., Speizer, F. E. and Willett, W. C. 1998. Multivitamin use, folate and colon cancer in women in the nurses health study. Annals of Internal Medicine. 129(7):517-524

389. Glenn, J. D., Xue, P. and Whartenby, A. K. 2018. Gemcitabine directly inhibits effector CD4 T cell activation and prevents experimental autoimmune encephalomyelitis. Journal of Neuroimmunology. 316: 7-16, https: // doi.org/10.1016/j. jneuroim.2017.12.002

390. Glynn, S. A., Albanes, D., Pietinen, P., Brown, C. C., Rautalahti, M., Tangrea, J. A., Gunter, E. W., Barrett, M. J., Virtamo, J. and Taylor, P. R. 1996. Colorectal cancer and folate status: a nested case-control study among male smokers. Cancer Epidemiol Biomarkers. 5(7):487-494

391. Goel, H. L. and Mercurio, A. M. 2013. VEGF targets the tumour cell. Nat Rew Cancer. 13(2): 871-882

392. Gogos, A.C., Ginopoulos, P., Salsa, B., Apostolidou, E., Zoumbos, C.N. and Kalfarentzos, F. 1998. Dietary omega-3 polyunsaturated fatty acids plus vitamin E restore

immunodeficiency and prolong survival for reversibly ill patients with generalized malignancy. Cancer. 82(2): 395–402.

393. Golovko, O., Nazarova, N. and Tuohimaa, P. 2005. Vitamin D-induced up-regulation of tumour necrosis factor alpha (TNF-α) in prostate cancer cells. Life Sciences. 77(5): 562-577

394. Gomaa, A. M. S. and Abd El-Aziz, E. A. 2016. Omega-3 fatty acids decreases oxidative stress, tumor necrosis factor-alpha, and interleukin-1 beta in hyperthyroidism-induced hepatic dysfunction rat model. Pathophysiology. 23(4): 295-301

395. Gong, Z., Holly, E. A. and Bracci, P. M. 2009. Intake of folate, vitamins B_6, B_{12} and methionine and risk of pancreatic cancer in a large population based case control study. Cancer Causes Control. 20(8):1317-1325

396. Gonzales-Rubio., Linares, C. I., Aguilar-Melero, P., Rodriguez-Peralvarez, M., Montero-Alvarez, J. L., de la Mata, M. and Ferrin, G. 2016. AP-1 inhibition by SR 11302 protects human hepatoma HepG2 cells from bile acid-induced cytotoxicity by restoring the NOS-3 expression. PlosOne. 11(8): e0160525, doi: 10.1371/journal.pone.0160525, 16 pages

397. Goodman, G. E., Schaffer, S., Omenn, G. S., Chen, C. and King, I. 2003. The association between lung and prostate cancer risk, and serum micronutrients. Results and Lessons learned from B carotene and retinol efficacy trial. Cancer Epidemiol Biomarkers Prev. 12(6): 518-526

398. Gopinath, S. D., Webb, A. E., Brunet, A. and Rando, T. A. 2014. Foxo3 promotes quiescence in adult muscle stem cells during the process of self-renewal. Stem Cell Reports. 2(4): 414-26

399. Gorgani, L., Mohammadi, M., Najafpour, G. D. and Nikzad, M. 2017. Piperine-the bioactive compound of black pepper: from isolation to medicinal formulations. Comprehensive Reviews in Food Science and Food Safety. 16:124-140, https:// doi.org/10.1111/1541-4337.12246

400. Görlach, A. and Bonello 2008. The cross-talk between NF-kappaB and HIF-1: further evidence for a significant liaison. Biochem. 412(3): e17-9, doi: 10.1042/BJ20080920

401. Gosselin, R., Hodge, H., Smith, R. and Gleason, M. 1976. Clinical Toxicology of Commercial Products. Fourth Edition. Baltimore: Williams and Wilkins, 1976
402. Gravina, G. L., Mancini, A., Scarsella, L., Colapietro, A., Jitariuc, A., Vitale, F., Marampon, F., Ricevuto, E. and Festuccia, C. 2016. Dual PI3K/mTOR inhibitor, XL765 (SAR245409), shows superior effects to sole PI3K [XL147 (SAR245408)] or mTOR [rapamycin] inhibition in prostate cancer cell models. Tumour Biol. 37: 341-51, doi: 10.1007/s13277-015-3725-3
403. Greenberg, M. D. 1980. The case against laetrile. The fraudulent cancer remedy. Cancer. 45(4): 799-807
404. Greenhough, A., Smartt, J. M. H., Moore, E. A., Roberts, R. H., Williams, A. C., Paraskeva, C. and Kaidi, A. 2009. The COX-2/PGE2 pathway: key roles in the hallmarks of cancer and adaptation to the tumour microenvironment. Carcinogenesis. 30(3): 377-386
405. Griffin, E. G. 1997. World without cancer: the story of vitamin B17. Publisher: Westlake Village, CA: American Media. 2nd Ed. 580 pages.
406. Grimshaw, K. M., Hunter, L. J., Yap, T. A., Heaton, S. P., Walton, M. I., Woodhead, S. J., Fazal, L., Reule, M., Davies, T. G., Seavers, L C., Lock, V., Lyons, J. F., Thompson, N. T., Workman, P. and Garrett, M. D. 2010. AT7867 is a potent and oral inhibitor of AKT and p70S6 kinase that induces pharmacodynamic changes and inhibits human tumor xenograft growth. Mol Cancer Ther. 9(5): 1100-10
407. Grzanna, R., Phan, P., Polotsky, A., Lindmark, L. and Frondoza, C. G. 2004. Ginger extract inhibits beta-amyloid peptide-induced cytokine and chemokine expression in cultured THP-1 monocytes. J Altern Complement Med. 10(6): 1009-13
408. Gu, L., Kelm, M. A., Hammerstone, J. F., Beecher, G., Holden, J., Haytowitz, D., Gebhardt, S. and Prior, R. L. 2004. Concentrations of proanthocyanidins in common foods and estimations of normal consumption. The Journal of Nutrition. 134(3): 613-617

409. Guerin, M., Sabatier, R. and Gonçalves, A. 2015. Trastuzumab emtansine (Kadcyla ®)) approval in Her2-positive metastatic breast cancers. Bull Cancer. 102(4): 390-7
410. Guha, P., Dey, A., Sen, R., Chatterjee, M., Chattopadhay, S. and Bandyopadhyay, S. K. 2011. Intracellular GSH depletion triggered mitochondrial Bax translocation to accomplish resveratrol-induced apoptosis in the U937 cell line. The Journal of Pharmacology and Environmental Therapeutics. 336(1): 206-214
411. Gunnell, M. L., Jonason, H. J., Loiselle, E. A., Kohn, A., Schwarz, M. E., Hilton, J. M. and O'Keefe, J. R. 2010. TAK1 regulates cartilage and joint development via the MAPK and BMP signaling pathways. J Bone Miner Res. 25(8): 1784-1797
412. Guo, A., He, D., Xu, H., Geng, C. and Zhao, J. 2015. Promotion of regulatory T cell induction by immunomodulatory herbal medicine licorice and its two constituents. Scientific Reports. 5: 14046, doi: 10.1038/srep14046, 12 pages.
413. Guo, H., Lee, J. D., Uzui, H., Yue, H., Wang, J., Toyoda, K., Geshi, T. and Ueda, T. 2006. Effects of folic acid and magnesium on the production of homocyteine-induced extracellular matrix metalloproteinase-2 in cultured rat vascular smooth muscle cells. Circ J. 70(1): 141-6, https://dopi.org/10.1253/circj.70.141
414. Guo, L., Zhang, H. and Chen, B. 2017. Nivolumab as programmed death-1(PD-1) inhibitor for targeted immunotherapy in tumor. J Cancer. 8(3): 410-416
415. Guo, P. and Feng, Y. 2017. Anti-inflammatory effects of kaempferol, myricetin, fisetin and ibuprofen in neonatal rats. Tropical Journal of Pharmaceutical Research. 16(8): 1819-1826
416. Guo, Y., Nemeth, J. A., O'Brien, C., Susa, M., Liu, X., Zhang, Z., Choy, E., Mankin, H., Hornicek, F. J. and Duan, Z. 2010. Effects of siltuximab on the IL6 induced signaling pathway in ovarian cancer. Clinical Cancer Research. 16(23): 5759-69
417. Guo, Y., Xu, F., Lu, T., Duan, Z. and Zhang, Z. 2012. Interleukin-6 signaling pathway in targeted therapy for cancer. Cancer Treat Rev. 38(7): 904-10

418. Gupta, P., Zhang, Y. K., Zhang, X. Y., Wang, Y. J., Lu, K. W., Hall, T., Peng, R., Yang, D. H., Xie, N. and Chen, Z. S. 2018. Voruciclib, a potent CDK4/6 inhibitor antagonizes ABCB1 and ABCG2-mediated multi-drug resistance in cancer cells. Cellular Physiology and Biochemistry. 45(4): 1515-1528
419. Gurchot, C. 1975. The trophoblast theory of cancer (John Beard, 1857-1924) revisited. Oncology. 31(5-6): 310-33
420. Gurgis, F. M. S., Heng, B., Wong, C., Adams, S., Guillemin, G. J., Johns, T. G., Chircop, M. and Munoz, L. 2015. Cytotoxic activity of the MK2 inhibitor CMPD1 in glioblastoma cells is independent of MK2. Cell Death Discovery. 1:15028, doi: 10.1038/cddiscovery.2015.28, 11 pages
421. Gutierrez-Venegas, G. and Gonzalez-Rosas, Z. 2017. Apigenin reduce lipoteichoic acid-induced inflammatory response in rat cardiomyoblast cells. Archives of Pharmacol Research. 40(2): 240-249
422. Gutierrez-Venegas, G., Luna, O. A., Ventura-Arroya, J. and Hernandez-Bermudez, C. 2013. Myricetin suppresses lipoteichoic acid-induced interleukin-1β and cyclooxygenase-2 expression in human gingival fibroblasts. Microbiology and Immunology. 57: 849-856, doi: 10.1111/1348-0421.12103
423. Haas, M. J., Jafri, M., Wehmeier, K. R., Onstead-Haas, L. M. and Mooradian, A. D. 2016. Inhibition of endoplasmic reticulum stress and oxidative stress by vitamin D in endothelial cells. Free Radical Biology and Medicine. 99: 1-10, http: // dx.doi.org / 10.1016 / j. freeradbiomed. 2016.07.020, 10 pages
424. Haddad, F. N., Teodoro, J. A., de Oliveira, L. F., Soares, N., de Mattos, M. R., Hecht, F., Dezonne, S. R., Vairo, L., de Mattos, M. R., Hecht, F., Dezonne, S. R., Vairo, L., Goldenberg, S. C. R., Gomes, A. C. F., de Carvalho, D. P., Gadelha, R. M., Nasciutti, E. L. and Miranda-Alves, L. 2013. Lycopene and beta-carotene induce growth inhibition and proapoptotic effects on ACTH-secreting pituitary adenoma cells. PlusOne. 8(5): e62773, doi: 10.1371 / journal. pone. 0062773, 12 pages
425. Hahm, E. and Singh, S. V. 2011. Sulforaphane inhibits constitutive and interleukin 6 induced activation of signal

transducer and activator of transcription 3 in prostate cancer cells. Cancer Prev Res (Phila). 3(4): 484-494

426. Hahm, E., Chandra-Kuntal, K., Desai, D., Amin, S. and Singh, V. S. 2012. Notch activation is dispensable for D,L-Sulforaphane mediated inhibition of human prostate cancer cell migration. Plos One. 7(9): e44957, doi: 10.1371/journal.pone.0044957, 11 pages

427. Hahn, H., Wicking, C., Zaphiropoulous, P. G., Gailani, M. R., Shanley, S., Chidambaram, A., Vorechovsky, I., Holmberg, E., Unden, A. B., Gillies, S., Negus, K., Smyth, I., Pressman, C., Leffell, D. J., Gerrard, B., Goldstein, A. M., Dean, M., Toftgard, R., Chenevix-Trench, G., Wainwright, B. and Bale, A. E. 1996. Mutations of the human homolog of Drosophila patched in the nevoid basal cell carcinoma syndrome. Cell. 85(6): 841-51

428. Halimah, E., Diantini, A., Destiani, D. P., Pradipta, I. S., Sastramihardja, H. S., Lestari, K., Subarnas, A., Abdulah, R. and Koyama, H. 2015. Induction of caspase cascade pathway by kaempferol-3-O-rhamnoside in LNCaP prostate cancer cell lines. Biomed Rep. 3(1): 115-117

429. Hamid, O., Chow, L. Q., Sanborn, R. E., Marshall, S., Black, C., Gribbin, M., McDevitt, J., Karakunnel, J. J. and Gray, J. E. 2016. Combination of MED10680, an anti-PD-1 antibody with durvalumab, an anti-PD-L1 antibody: A phase 1, open-label study in advanced malignancies. Annals of Oncology. 27(Suppl-6): vi359-vi378, doi: 10.1093/annonc/mdw378.5

430. Hamilton, E. and Infante, J. R. 2016. Targeting CDK4/6 in patients with cancer. Cancer Treatment Reviews. 45:129-138, http://dx.doi.org/10.1016/j.critrevonc.2017.02.022

431. Hammer, J. B., Dickson, P. V., Sims, T. L., Zhou, J., Spence, Y., Ng, C. Y. and Davidoff, A. M. 2007. Bortezomib inhibits angiogenesis and reduces tumor burden in a murine model of neuroblastoma. Surgery. 142(2): 185-91

432. Han, K. S., Li, N., Raven, P. A., Li, E., Fazli, L., Gleave, M. E. and So, A. I. 2013. ER stress protein GRP78 as a therapeutic target combined with antiangiogenmic therapy in renal cell carcinoma. J Clin Oncol. Genitourinary Cancers Symposium.

Suppl 6; Abstract No: 428, Category: Genitourinary Cancer. Subcategory: Renal Cell Cancer

433. Hanker, A., Healy, K., Nichols, J. and Der, C. 2009. Romidepsin inhibits Ras-dependent growth transformation of NIH 3T3 fibroblasts and RIE-I epithelial cells independently of RAS signaling inhibition. Journal of Molecular Signaling. 4:5, doi: 10.1186/1750-2187-4-5, 13 pages

434. Hann, H. L., Stahlhut, M. W. and Blumberg, B. S. 1998. Iron nutrition and tumor growth: Decreased tumor growth in iron-deficient mice. Cancer Research. 48(15): 4168-4170

435. Hansen, L. T., Thylejaer, T., Orntoft, T. G. and Petersen, L. N. 2003. The role of mismatch repair in small-cell lung cancer cells. European Journal of Cancer. 39(10): 1456-67

436. Haque, R. M. and Bradbury, H. J. 2002. Total cyanide determination of plants and foods using the picrate and acid hydrolysis methods. Food Chemistry. 77(1): 107-114

437. Hara, A., Sasazuki, S., Inoue, M., Shimazu, T., Iwasaki, M., Sawada, N., Yamaji, T., Ishihara, J., Iso, H., Tsugane, S. and the Japan Public Health Center-Based Prospective Study Group. 2011. Use of vitamin supplements and risk of total cancer and cardiovascular disease among the Japanese general population: A population-based survey. BMC Public Health. 11(1):540-550 doi: 10.1186/1471-2458-11-540

438. Hara, T., Kojima, T., Matsuzaki, H., Nakamura, T., Yoshida, E., Fujiwara, Y., Yamamoto, C., Saito, S. and Kaji, T. 2017. Induction of syndecan-4 by organic-inorganic hybrid molecules with a 1,10-Phenanthroline structure in cultured vascular endothelial cells. Int J Mol Sci. 18(2): 352-365

439. Harada, H. and Grant, S. 2012. Targeting the regulatory machinery of BIM for cancer tharpy. Crit Rev Eukaryot Gene Expr. 22(2): 117-29

440. Harakeh, S., Diab-Assaf, M., Khalife, J. C., Abu-EL-Ardat, A. K., Baydoun, E., Niedzwiecki, A., El-Sabban, M. E. and Rath, M. 2007. Ascorbic acid induces apoptosis in adult T-cell leukemia. Anticancer Research. 27(1A): 289-298

441. Harakeh, S., Khalife, J., Baydoun, E., Azar, R., Al-Hejin, A., Barbour, E., Azhar, E., Niedzwiecki, A., Al Jaouni, S., Diab-Assaf, M., Ma. K. and Rath, M. 2018. Effects of ascorbic acid on tax, NF-kB and MMP-9 in human T-cell lymphotropic virus type 1 positive malignant T-lymphocytes. Anticancer Agents Med Chem. 18(2): 237-244

442. Harbeck, N., Beckmann, M. W., Rody, A., Schneeweiss, A., Müller, V., Fehm, T., Marschner, N., Gluz, O., Schrader, I., Heinrich, G., Untch, M. and Jackisch, C. 2013. HER2 dimerization inhibitor pertuzumab-mode of action and clinical data in breast cancer. Breast Care (Basel). 8(1): 49-55, doi: 10.1159/000346837.

443. Hardman, W.E. 2004. (n-3) fatty acids and cancer therapy. Journal of Nutrition. 134(12): 3427–3430

444. Harnack, L., Jacobs, D. R. Jr., Nicodemus, K., Lazovich, D., Anderson, K. and Folsom, A. R. 2002. Relationship of folate, vitamin B-6, vitamin B-12 and methionine intake of incidence of colorectal cancers. Nutr Cancer. 43(2):152-8

445. Harnly, J. M., Doherty, R. F., Beecher, G. R., Holden, J. M., Haytowitz, D. B., Bhagwat, S. and Gebhardt, S. 2006. Flavonoid content of U.S. fruits, vegetables, and nuts. J Agric Food Chem. 54(26): 9666-77

446. Harsha Raj M., Ghosh, D., Banerjee, R. and Salimath B. P. 2017. Suppression of VEGF-induced angiogenesis and tumor growth by *Eugenia jambolana, Musa paradisiaca,* and *Coccinia indica* extracts 55(1): 1489–1499 doi: 10.1080/13880209.2017.1307422

447. Hartman, C. Z., Yang, X., Glass, O., Lei, G., Osada, T., Dave, S. S., Morse, A. M., Clay, M. T. and Lyerly, K. H. 2011. HER2 overexpression elicits a pro-inflammatory IL-6 autocrine signaling loop that is critical for tumorigenesis. Cancer Res. 71(13): 4380-4391

448. Hartman, J. T., Albanes, D., Rautalahti, M., Tangrea, A. J., Virtamo, J., Stolzenberg, R. and Taylor, R. P. 1998. Physical activity and prostate caner in the alpha-tocopherol, beta-carotene (ATBC) cancer prevention study (Finland). Cancer Causes and Control. 9(1): 11-8, PMID:9486459

449. Hasegawa, K., Ichikawa, W., Fujita, T., Ohno, R., Okusa, T., Yoshinaga, K. and Sugihara, K. 2001. Expression of cyclooxygenase-2 (COX-2)mRNA in human colorectal adenomas. Eur J Cancer. 37(12): 1469-74

450. Hashemzaei, M., Far, A. D., Yari, A., Heravi, R. E., Tabrizian, K., Taghdisi, S. M., Sadegh, S. E., Tsarouhas, K., Kouretas, D., Tzanakakis, G., Nikitovic, D., Anisimov, N. Y., Spandidos, D. A., Tsatsakis, A. M. and Rezaee, R. 2017. Anticancer and apoptosis-inducing effects of quercetin in vitro and in vivo. Oncol Rep. 38(2): 819-828

451. Hassan, R., Thomas, A., Patel, R. M., Nemunaitis, J. J., Bennouna, J. and Powderly, D. J. 2016. Avelumab (MSB0010718C; anti-PD-L1) in patients with advanced unresectable mesothelioma from the javelin solid tumor phase Ib trial: Safety, clinical activity, and PD-L1 expression. Journal of Clinical Oncology. 34(Suppl. 15): 8503-8503, doi: 10.1200/JCO.2016.34.15_suppl.8503

452. Hayakawa, M., Kaizawa, H., Moritomo, H., Koizumi, T., Ohishi, T., Okada, M., Ohta, M., Tsukamoto, S., Parker, P., Workman, P. and Waterfield, M. 2006. Synthesis and biological evaluation of 4-morpholino-2-phenylquinazolines and related derivatives as novel PI3 kinase p110α inhibitors. Bioorganic and Medicinal Chemistry. 14(20): 6847-6858

453. Hayakawa, T., Sugiyama, J., Yaguchi, T., Imaizumi, A. and Kawakami, Y. 2014. Enhanced anti-tumor effects of the PD-1/PD-L1 blockade by combining a highly absorptive frm of NF-kB/STAT3 inhibitor curcumin. Journal of Immunotherapy of Cancer. 2(Suppl 3): P210-P210

454. He, B., Gao, J., Zhang, B., Luo, Q., Shi, Q., Kim, S. H., Huang, E., Gao, Y., Yang, K., Wagner, E. R., Wang, L., Tang, N., Luo, J., Liu, X., Li, M., Bi, Y., Shen, J., Luther, G., Hu, N., Zhou, Q., Luu, H. H., Haydon, R. C., Zhao, Y. and He, T. 2011. Tetrandrine inhibits Wnt/β-catenin signaling and suppresses tumor growth of human colorectal cancer. Mol Pharmacol. 79(2): 211-219

455. He, G., Dhar, D., Nakagawa, H., Font-Burgada, J., Ogata, H., Jiang, Y., Shalapour, S., Seki, E., Yost, S. E., Jepsen, K.,

Frazer, K. A., Harismendy, O., Hadziapostolou, M., Liopoulos, D., Suetsugu, A., Hoffman, R. M., Tateishi, R., Koike, K. and Karin, M. 2013. Identification of liver cancer progenitors whose malignant progression depends on autocrine IL-6 signaling. Cell. 155(2): 384-96

456. He, H. L., Ji, L. J., Li, Q. Z., Zhang, R., Huang, J. M. and Li, G. 2015. Effect of quercetin on doxorubicin-induced expression of MDR1 gene in HL-60 cells. Zhongguo Shi Yan Xue Ye Xue Za Zhi. 23(1): 70-6, doi: 10.7534/j.issn.1009-2137.2015.01.014

457. He, L., Luo, L., Zhu, H., Yang, H., Zhang, Y., Wu, H., Sun, H., Jiang, F., Kathera, C. S., Liu, L., Zhuang, Z., Chen, H., Pan, F., Hu, Z., Zhang, J. and Guo, Z. 2017. FEN1 promotes tumor progression and confers cisplatin resistance in non-small-cell lung cancer. Mol Oncol. 11(6): 640-654

458. He, M., Zhang, L. L., Li, L., Shen, Y., Lin, L., Zheng, W., Chen, L., Bian, X., Ng, H. and Tang, L. 2014. Curcumin suppresses cell proliferation through inhibition of the Wnt/β-catenin signaling pathway in medulloblastoma. 32(1): 173-180, https://doi.org/10.3892/or.2014.3206

459. He, W., Ma, X., Yang, X., Zhao, Y., Qiu, J. and Hang, H. 2011. A role for the arginine methylation of Rad9 in checkpoint control and cellular sensitivity to DNA damage. Nucleic Acid Res. 39(11): 4719-4727

460. He, X., Lin, H., Yuan, L. and Li, B. 2017. Combination therapy with L-arginine and αPD-L1 antibody boosts immune response against osteosarcoma in immunocompetent mice. Cancer Biology & Therapy. 18(2): 94-100

461. Heinen, M. M., Verhage, B. A., Goldbohm, R. A. and van den Brandt, P. A. 2012. Intake of vegetables, fruits, carotenoids and vitamins C and E and pancreatic cancer risk in The Netherlands cohort study. IJC (International Journal of Cancer). 130(1):147-158, doi: 10.1002/ijc.25989

462. Heinonen, O. P., Albanes, D., Virtamo, J., Taylor, P. R., Huttunen, J. K., Hartman, A. M., Haapakoski, J., Malila, N., Rautalahti, M., Ripatti, S., Maenpaa, H., Teerenhovi, L., Koss, L., Virolainen, M. and Edwards, B. K. 1998. Prostate cancer and

supplementation with α-tocopherol and β-caroten: Incidence and mortality in controlled trial. J Natl Cancer Inst. 90(6): 440-446

463. Heinzelmann, J., Henning, B., Sanjmyatav, J., Posorski, N., Steiner, T., Wunderlich, H., Gajda, M. R. and Junker, K. 2012. Specific miRNA signatures are associated with metastasis and poor prognosis in clear cell renal carcinoma. World J Urol. 29(3): 367-73

464. Hendriks, D., He, Y., Koopmans, I., Wiersma, V. R., van Ginkel, R. J., Samplonius, D. F., Helfrich, W. and Bremer, E. 2016. Programmed death ligand 1 (PD-L1)-targeted TRAIL combines PD-L1-mediated checkpoint inhibition with TRAIL-mediated apoptosis induction. Oncoimmunology. 5(8): e1202390, doi: 10.1080/2162402x.2016.1202390, 13 pages

465. Heneman, K. and Zidenberg-Cherr, S. 2008. Nutrition and Health Info-Sheet. UC Cooperative Extension Center for Health and Nutrition Research. Department of Nutrition, University of California Davis, CA 95616-8669, 2 pages

466. Hennigan, S. and Kavanaugh, A. 2008. Interleukin-6 inhibitors in the treatment of rheumatoid arthritis. Ther Clin Risk Manag. 4(4): 767-775

467. Herbst, S. R., Soria, J., Kowanetz, M., Fine, D. G., Hamid, O., Gordon, S. M., Sosman, A. J., McDermott, F. D., Powderly, D. J., Gettingen, N. S., Kohrt, K. E. H., Horn, L., Lawrence, P. D., Rost, S., Leabman, M., Xiao, Y., Mokatrin, A., Koeppen, H., Hegde, S. P., Mellman, I., Chen, S. D. and Hodi, S. F. 2014. Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients. Nature. 515(7528): 563-567

468. Hernandez Losa. J., Parado Cobo, C., Guniea Viniegra, J., Sanchez-Arevalo, L. V. J., Ramon, Y. C. S. and Sanchez-Prieto, R. 2003. Role of the p38 MAPK pathway in cisplatin-based therapy. Oncogene. 22(26): 3998-4006

469. Hernandez, P., Gronke, K. and Diefenbach, A. 2017. A catch-22: Interleukin-22 and cancer. European Journal of Immunology. 48(1): 15-31, doi: 10.1002/eji.201747183

470. Hettmer, S., Teot, L. A., van Hummelen, P., MacConaill, L., Bronson, R. T., Dall'Osso, C., Mao, J., McMahon, P., Gruber,

P. J., Grier, H.E., Rodriguez-Galindo, C., Fletcher, C. D. and Wagers, A. J. 2013. Mutations in Hedgehog pathway genes in fetal rhabdomyomas. Journal of Pathology. 231(1): 244-52, doi:10.1002/path.4229

471. Hickinson, D. M., Klinowska, T., Speake, G., Vincent, J., Trigwell, C., Anderton, J., Beck, S., Marshall, G., Davenport, S., Callis, R., Mills, E., Grosios, K., Smith, P., Barlaam, B., Wilkinson, R. W. and Ogilvie, D. 2010. AZD8931, an equipotent, factor receptor, ERBB2 (HER2), and ERBB3: a unique agent for simultaneous ERBB receptor blockade in cancer. Clin Res. 16(4): 1159-69

472. Hill, G. J., Shine, T. E., Hill, H. Z. and Miller, C. 1976. Failure of amygdalin to arrest B_{16} melanoma and BW5147 AKR leukemia. Cancer Research. 36(6): 2102-2107

473. Hill, R. J., Dabbagh, K., Phippard, D., Li, C., Suttmann, R. T., Welch, M., Papp, E., Song, K. W., Chang, K. C., Leaffer, D., Kim, Y. N., Roberts, R. T., Zabka, T. S., Aud, D., Dal Porto, J., Manning, A. M., Peng, S. L., Goldstein, D. M. and Wong, B. R. 2008. Pamapimod, a novel p38 mitogen-activated protein kinase inhibitor: preclinical analysis of efficacy and selectivity. J Pharmacol Exp Ther. 327(3): 610-9

474. Hirata, H., Ueno, K., Nakajima, K., Tabatabai, Z. L., Hinoda, Y., Ishii, N. and Dahiya, R. 2013. Genistein downregulates onco-miR-1260b and inhibits Wnt-signallling in renal cancer cells. Bt J Cancer. 108(10): 2070-2078

475. Hirosawa, M., Nakahara, M., Otosaka, R., Imoto, A., Okazaki, T. and Takahashi, S. 2009. The p38 pathway inhibitor SB202190 activates MEK/MAPK to stimulate the growth of leukemia cells. Leuk Res. 33(5): 693-9

476. Hirvonen, T., Virtamo, J., Korhonen, P., Albanes, D. and Pietinen, P. 2001. Flavonol and flavone intake and the risk of cancer in male smokers (Finland). Cancer Causes and Control. 12(9): 789-796

477. Hnia, K., Gayraud, J., Hugon, G., Ramonatxo, M., De La Porte, S., Matecki, S. and Mornet, D. 2008. L-Arginine decreases inflammation and modulates the nuclear factor-kB/matrix

metalloproteinase cascade in Mdx muscle fibers. The American Journal of Pathology. 172(6): 1509-1519

478. Ho, J., Jun, W., Choue, R. and Lee, J. 2012. I3C and ICZ inhibit migration by suppressing the EMT process and FAK expression in breast cancer cells. Molecular Medicine Reports. 7(2): 384-388

479. Ho, W. T., Exton, J. H. and Williger, B. T. 2003. Arfaptin 1 inhibits ADP-ribosylation factor-dependent matrix metalloproteinase-9 secretion induced by phorbol ester in HT 1080 fibrosarcoma cells. FEBS Lett. 537(1-3): 91-5

480. Hoch, L., Faure, H., Roudaut, H., Schoenfelder, A., Mann, A., Girard, N., Bihannic, L., Ayrault, O., Petricci, E., Taddei, M., Rognan, D. and Ruat, M. 2015. MRT-92 inhibits Hedgehog signaling by blocking overlapping binding sites in the transmembrane domain of the smoothened receptor. The FASEB Journal. 29(5): 1817-1829

481. Hoellenriegel, J., Meadows, A. S., Sivina, M., Wierda, G. W., Kantarjian, H., Keating, M., Giese, N., O'Brien, S., Yu, A., Miller, L. L., Lannutti, J. B. and Burger, A. J. 2015. The phosphoinositide 3-kinase delta inhibitor, CAL-101, inhibits B-cell receptor signaling and chemokine networks in chronbic lympocytic leukemia. Blood. 118(13): 3603-3612

482. Hoelzl, C., Glatt, H., Meinly, W., Sontaq, G., Haidinger, G., Kundi, M., Simic, T., Chakraborty, A., Bichler, J., Ferk, F., Angelis, K., Nersesyan, A. and Knasmüller, S. 2008. Consumption of Brussels sprouts protects peripheral human lymphocytes against 2-amino-1-methyl-6-phenylimidazol [4,5-6]pyridine (PhIP) and oxidative DNA-damage:results of a controlled human intervention trial. Mol Nutr Food Res. 52(3):330-41

483. Hoensch, H., Groh, B., Edler, L. and Kirch, W. 2008. Prospective cohort comparison of flavonoid treatment in patients with resected colorectal cancer to prevent recurrence. World J Gastroenterol. 14(14): 2187-2193

484. Hofmann, J., Gekeler, V., Ise, W., Moller, A., Mitterdorfer, J., Hofer, S., Utz, I., Gotwald, M., Boer, R., Glossmann, H. and Grunicke, H. H. 1995. Mechanism of action of

dexniguldipine-HCL (B8509-035), a new potent modulator of multidrug resistance. Biochemical Pharmacology. 49(5): 603-609

485. Hogan, F. S., Krishnegowda, N. K., Mikhailova, M. and Kahlenberg, M. S. 2007. Flavonoid, silibinin, inhibits proliferation and promotes cell-cycle arrest of human colon cancer. J Surg Res. 143(1): 58-65, doi:10.1016/j.jss.2007.03.080

486. Holczer, M., Besze, B., Zambo, B., Csala, M., Banhegyi, G. and Kapuy, O. 2018. Epigallocatechin-3-gallate (EGCG) promotes autophagy-dependent survival via influencing the balance of mTOR-AMPK pathways upon endoplasmic reticulum stress. Oxidative Medicine and Cellular Longevity. Vol. 2018, Article ID: 6721530, http://doi.org/10.1155/2018/6721530, 16 pages

487. Holick, N. C., Michaud, S. D., Stolzenberg-Solomon, R., Mayne, T. S., Pietinen, P., Taylor, R. P., Virtamo, J. and Albanes, D. 2002. Dietary carotenoids, serum β-carotene, and retinol and risk of lung cancer in the alpha-tocopherol, beta carotene cohort study. Am J Epidemiol. 156(6): 536-547

488. Holven, B. K., Haugstad, S. T., Holm, T., Aukrust, P., Ose, L. and Nenseter, M. S. 2002. Folic acid treatment reduces elevated plasma levels of asymmetric dimethylarginine in hyperhomocysteinaemic subjects. British Journal of Nutrition. 89: 359-363, doi: 10.1079/BJN2002779

489. Hope, C., Kestutis, P., Marina, P., Moyer, M. P., Johal, K. S., Woo, J., Santoso, C., Hanson, J. A. and Holcombe, R. F. 2008. Low concentrations of resveratrol inhibit Wnt signal throughput in colon-derived cells: Implications for colon cancer prevention. Mol Nutr Food Res. 52(Suppl 1): S52-S61

490. Horiguchi, A., Asano, T., Kuroda, K., Sato, A., Asakuma, J., Ito, K., Hayakawa, M., Sumitomo, M. and Asano, T. 2010. STAT3 inhibitor WP1066 as a novel therapeutic agent for renal cell carcinoma. Br J Cancer. 102(11): 1592-9

491. Hossain, T., Rashid, A. and Alam, T. 2013. Screening of Bangladeshi vegetables for peroxidase. International Journal of Pharmaceutical Sciences and Research (IJPSR). 4(5):1934-1939

492. Hou, T., Lin, J., Wen, H., Chen, L., Hsu, S. P. and Lee, W. 2013. Folic acid inhibits endothelial cell migration through inhibiting the RhoA activity mediated by activating the folic acid receptor/cSrc/p190RhoGAP-signaling pathway. Biochemical Pharmacology. 85(3): 376-384
493. Hou, X., Bai, X., Gou, X., Zeng, H., Xia, C., Zhuang, W., Chen, X., Zhao, Z., Huang, M. and Jin, J. 2015. 3,4,5,5,7-pentamethoxyflavone sensitizes cisplatin-resistant A549 cells to cisplatin by inhibition of Nrf2 pathway. Mol Cells. 38(5): 396-401
494. Houghton, C. A., Fassett, R. G. and Coombes, J. S. 2016. Sulforaphane and other nutrigenomic Nrf2 activators: can the clinician's expectation be matched by the reality? Oxid Med Cell Longev. 2016: 7857186, doi: 10.1155/2016/7857186, 17 pages
495. Hsiao, G., Lee, T., Jan, J., Hsiao, C. and Cheng, Y. 2013. Heat shock protein 90 inhibitor radicicol attenuates matrix metalloproteinase expression in human monocytic cells (P4153). The Journal of Immunology. Meeting Abstract Supplement. 190, 112.10
496. Hsieh, C., Hall, K., Ha, T., Li, C., Krishnaswamy, G. and Chi, S. D. 2007. Baicalein inhibits IL-1β and TNF-α-induced inflammatory cytokine production from human mast cells via regulation of the NF-kB pathway. Clin Mol Allergy. 5:5, doi: 10.1186/1476-7961-5-5, 10 pages
497. Hsieh, C., Hsiao, G., Hsu, M., Wang, Y. and Sheu, J. 2014. PMC, a potent hydrophilic α-tocopherol derivative, inhibits NF-kB activation via pp2A but not IkBα-dependent signals in vascular smooth muscle cells. J Cell Mol Med. 18(7): 1278-1289
498. Hsu, A. L., Ching, T. T., Wang, D. S., Song, X., Rangnekar, V. M. and Chen, C. S. 2000. The cyclooxygenase-2 inhibitor celecoxib induces apoptosis by blocking Akt activation in human prostate cancer cells independently of Bcl-2. J Biol Chem. 275(15): 11397-403
499. Hsu, Y., Wolter, G. K. and Youle, J. R. 1997. Cytosol-to-membrane redistribution of Bax and Bcl-xL during apoptosis. PNAS. 94(8): 3668-3672

500. Hu, L., Gao, Y., Cao, Y., Zhang, Y., Xu, M., Wang, Y., Jing, Y., Guo, S., Jing, F., Hu, X. and Zhu, Z. 2016. Association of plasma arginine with breast cancer molecular subtypes in women of Liaoning province. International Union of Biochemistry and Molecular Biology. 68(12): 980-984
501. Hu, Q., Peng, J., Liu, W., He, X., Cui, L., Chen, X., Yang, M., Liu, H., Liu, S. and Wang, H. 2014. Lin28B is a novel prognostic marker in gastric adenocarcinoma. Int J Clin Exp Pathol. 7(8): 5083-92
502. Hu, T., Chung, Y. M., Guan, M., Ma, M., Ma, J., Berek, J. S. and C-T. Hu, M. 2014. Reprogramming ovarian and breast cancer cells into non-cancerous cells by low-dose metformin or SN-38 through FOXO3 activation. Scientific Reports. 4: 5810, doi: 10.1038/srep05810, 13 pages.
503. Hu, Y. Y., Fu, L. A., Li, S. Z., Chen, Y., Li, J. C., Han, J., Liang, L., Li, L., Ji, C. C., Zheng, M. H. and Han, H. 2014. Hif-1α and Hif-2α differentially regulate Notch signaling through competitive interaction with the intracellular domain of Notch receptors in glioma stem cells. Cancer Lett. 349(1): 67-76, doi:10.1016/j.canlet.2014.03.035
504. Huang, C., Chan, C., Chou, I., Lien, C., Hung, H. and Lee, M. 2013. Quercetin induces growth arrest through activation of Foxo1 transcription factor in EGFR-overexpressing oral cancer cells. The Journal of Nutritional Biochemistry. 24(9): 1596-1603
505. Huang, C., Lii, C., Lin, A., Yeh, Y., Yao, H., Li, C. and Wang, T. 2013. Protection by chrysin, apigenin, and luteolin against oxidative stress is mediated by the Nrf2-dependent up-regulation of heme oxygenase 1 and glutamate cysteine ligase in rat primary hepatocytes. Archives of Toxicology. 87(1): 167-178, https://doi.org/10.1007/s00204-012-0913-4
506. Huang, D., Ding, Y., Zhou, M., Rini, I. B., Petillo, D., Qian, C., Kahnoski, R., Futreal, A. P., Furge, A. K. and The, T. B. 2010. Interleukin-8 mediates resistance to antiangiogenic agent sunitinib in renal cell carcinoma. Cancer Res. 70(3): 1063-1071
507. Huang, H. C., Huang, C. Y., Lin-Shiau, S. Y. and Lin, J. K. 2009. Ursolic acid inhibits IL-1beta or TNF-alpha-induced C6

glioma invasion through suppressing the association ZIP/p62 with PKC-zeta and downregulating the MMP-9 expression. Mol Carcinog. 48(6): 517-31

508. Huang, H., Alberg, J. A., Norkus, P. E., Hoffman, C. S., Comstock, W. G. and Helzlsouer, J. K. 2003. Prospective study of antioxidant micronutrients in the blood and the risk of developing prostate cancer. Am J Epidemiol. 157(4): 335-344

509. Huang, H., Rose, J. L. and Hoyt, D. G. 2004. p138 mitogen-activated protein kinase mediates synergistic induction of inducible nitric-oxide synthase by lipopolysaccharide and interferon-gamma through signal transducer and activator of transcription 1 ser727 phosphorylation in murine aortic endothelial cells. Mol Pharmacol. 66(2): 302-11

510. Huang, R., Yu, Y., Cheng, W., OuYang, C., Fu, E. and Chu, C. 2010. Immunosuppressive effect of quercetin on dendritic cell activation and function. The Journal of Immunology. 184(12): 6815-6821

511. Huang, X., He, Z., Jiang, X., Hou, M., Tang, Z., Zhen, X., Liang, Y. and Ma, J. 2016. Folic acid represses hypoxia-induced inflammation in THP-1 cells through inhibition of the PI3K/Akt/HIF-1α pathway. PlosOne. 11(3):e0151553, doi:10.1371/journal.pone.0151553, 15 pages

512. Huang, X., Zhang, L. and Zhang, Z. 2013. Crosstalk between endoplasmic reticulum stress and oxidative stress in apoptosis induced by α-tocopherol succinate in human gastric carcinoma cells. 109(4): 727-735

513. Huang, Y., Huang, D., Guh, J., Chen, I., Tzeng, C. and Teng, C. 2005. CIL-102 interacts with microtubule polymerization and causes mitotic arrest following apoptosis in the human prostate cancer PC-3 cell line. The Journal of Biological Chemistry. 280(4): 2771-2779

514. Huang, Y., Lin, L., Shanker, A., Malhotra, A., Yang, L., Dikov, M. M. and Carbone, D. P. 2011. Ressuscitating cancer immunosurveillance: selective stimulation of DLL1-Notch signaling in T cells rescues T cell function and inhibits tumor growth. Cancer Res. 71(19): 6122-6131

515. Huang, Y., Miao, Z., Hu, Y., Yuan, Y., Zhou, Y., Wei, L., Zhao, K., Guo, Q. and Lu, N. 2017. Baicalein reduces angiogenesis in the inflammatory microenvironment via inhibiting the expression of AP-1. Oncotarget. 8(1): 883-899, doi: 10.18632/oncotarget.13669
516. Huang, Y., Wang, Y., Li, Y., Guo, K. and He, Y. 2011. Role of sorafenib and sunitinib in the induction of expressions of NKG2D ligands in nasopharyngeal carcinoma 2ith high expression of ABCF2. Journal of Cancer Research and Clinical Oncology. 137(5): 829-837
517. Huerta-Yepez, S., Tirado-Rodriguez, A. B. and Hankinson, O. 2016. Role of diets rich in Omega-3 and Omega-6 in the development of cancer. Boletin Medico del Hospital Infantil de Mexico. 73(6): 446-456
518. Hughes, P. J., Lee, J. S., Reiner, N. E. and Brown, G. 2008. The vitamin D receptor-mediated activation of phosphatidylinositol 3-kinase (PI3Kalpha) plays a role in the 1 alpha, 25-dihydroxyvitamin D3-stimulated increase in steroid sulphatase activity in myeloid leukaemic cell lines. J Cell Biochem. 103(5): 1551-72
519. HUGO Gene Nomenclature Committee. 2017. MR101-1, microRNA 101-1 [Homo sapiens (human)]. Gene ID: 406893, Primary source; HGNC: HGNC: 31488
520. Huh, J., Choi, J., Shin, Y., Park, D., Kang, J. W., Nam, D., Choi, D. and Lee, J. 2014. Arginine enhances osteoblastogenesis and inhibits adipogenesis through the regulation of Wnt and NFATc signaling in human mesenchymall stem cells. Int J Mol Sci. 15(7): 13010-13029
521. Hulten, K., van Kappel, L. A., Winkvist, A., Kaaks, R., Hallmans, G., Lenner, P. and Riboli, E. 2001. Carotenoids, alpha-tocopherols, and retinol in plasma and breast cancer risk in northern Sweden. Cancer Causes and Control. 12(6): 529-537
522. Humphries, J. M. and Khachik, F. 2003. Distribution of lutein, zeaxanthin and related geometrical isomers in fruit, vegetables, wheat and pasta products. J Agric Food Chem. 51(5): 1322-1327

523. Hung, T., Chen, P., Wu, H., Wu, S., Tsai, P., Hsieh, Y. and Chang, H. 2017. Kaempferol inhibits the invasion and migration of renal cancer cells through the downregulation of Akt and Fak pathways. Int J Med Sci. 14(10): 984-993
524. Hunter, D. J., Manson, J. E., Colditz, G. A., Stampfer, M. J., Rosner, B., Hennekens, C. H., Speizer, F. E. and Willett, W. C. 1993. A prospective study of the intake of vitamins C, E and A and the risk of breast cancer. N Engl J Med. 329(4): 234-240
525. Huo, L., Shi, W., Chong, L., Wang, J., Zhang, K. and Li, Y. 2016. Asiatic acid inhibits left ventricular remodeling and improves cardiac function in a rat model of myocardial infection. Exp Ther Med. 11(1): 57-64, doi:10.3892/etm.2015.2871
526. Huo, X. W., Gao, Y. F. and Ma, Q. Y. 2010. Effect of L-arginine on human colon carcinoma cell line LS174 through NO pathway and the mechanism. Nan Fang Yi Ke Da Xue Xue Bao. 30(1): 70-5, doi: 10.3969/j.issn.1673-4254.2018.10.08
527. Hussain, K., Francois, R. A., Yamauchi, T., Perez, M., Sebti, M. S. and Malafa, M. T. 2011. Vitamin E δ-tocotrienol augments the antitumor activity of Gemcitabine and suppresses constitutive NF-kB activation in pancreatic cancer. Molecular Cancer Therapeutics. 10(12): 2363-2372
528. Hussain, S. P., Hofseth, L. J. and Harris, C. C. 2003. Radical causes of cancer. Nature Reviews Cancer. 3(4):276-285
529. Hutchinson, J., Burley, V. J., Greenwood, D. C., Thomas, J. D. and Cade, J. E. 2011. High dose vitamin C supplement use is associated with self-reported histories of breast cancer and other illnesses in the UK women's cohort study. Public Health Nutrition. 14(5):768-777
530. Hwang, H. J., Lee, H. J., Kim, C. J., Shim, I. and Hahm, D. H. 2008. Inhibitory effect of amygdalin on lipopolysaccharide-inducible TNF-alpha and IL-1beta mRNA expression and carrageenan-induced rat arthritis. J Microbiol Biotechnol. 18(10): 1641-7
531. Hwang, I. S., Lee, J. and Lee, D. G. 2011. Indole-3-carbinol generates reactive oxygen species and induces apoptosis. Biol Pharm Bull. 34(10): 1602-8

532. Hwang, S. Y., Kim, Y., Kim, M. O., Kang, M., Oh, S. W., Nho, Y. H., Park, S. and Lee, J. 2017. Cannabidiol upregulates through CB1 dependent pathway by activating p38 MAPK and p42/44 MAPK. Chemica-Biological Interactions. 273:107-114, https://doi.org/10.1016/j.cbi.2017.06.005

533. Hwang, Y. P. and Jeong, H. G. 2010. Metformin blocks migration and invasion of tumor cells by inhibition of matrix metalloproteinase-9 activation through a calcium and protein kinase Calpha-dependent pathway: phorbol-12-myristate-13-acetate-induced/extracellular signal-regulated kinase/activator protein-1. Bt J Pharmacol. 160(5): 1195-211

534. Ihle, N. T., Williams, R., Chow, S., Chew, W., Berggren, M. I., Paine-Murrieta, G, Minion, D. J., Halter, R. J., Wipf, P., Abraham, R., Kirkpatrick, L. and Powis, G. 2004. Molecular pharmacology and antitumor activity of Px-866, a novel inhibitor of phosphoinositide-3-kinase signaling. Mol Cancer Ther. 3(7): 763-72

535. Ikebuchi, R., Konnai, S., Okagawa, T., Yokoyama, K., Nakajima, C., Suzuki, Y., Murata, S. and Ohashi, K. 2014. Influence of PD-L1 cross-linking on cell death in PD-L1-expressing cell lines and bovine lymphocytes. Immunology. 142(4): 551-561

536. Ikeda, F., Doi, Y., Yonemoto, K., Ninomiya, T., Kubo, M., Shikata, K., Hata, J., Tanizaki, Y., Matsumoto, T., Iida, M. and Kiyohara, Y. 2009. Hyperglycemia increases risk of gastric cancer posed by *Helicobacter pylori* infection: a population based cohort study. Gastroenterology. 136(4): 1234-1241

537. Ikeda, H. O., Sasaoka, N., Koike, M., Nakano, N., Muraoka, Y., Toda, Y., Fuchigami, T., Shudo, T., Iwata, A., Hori, S., Yoshimura, N. and Kakizuka, A. 2014. Novel VCP modulators mitigate major pathologies of rd10, a mouse model of retinitis pigmentosa. Scientific Reports. 4: 5970, doi: 10.1038/srep05970, 9 pages

538. Iliopoulos, D., Hirsch, H. A. and Kevin Struhl. 2009. An epigenetic switch involving NF-κB, Lin28, let-7 microRNA, and IL6 links inflammation to cell transformation. Cell. 139(4): 693–706.

539. Illiopoulos, D., Hirsch, H. A. and Struhl, K. 2009. An epigenetic switch involving NF-kappaB, Lin28, Let-7 MicroRNA, and IL6 links inflammation to cell transformation. Cell. 139(4): 693-706
540. Iqbal, N. and Iqbal, N. 2014. Human epidermal growth factor receptor 2 (Her2) in cancers: Overexpression and therapeutic implications. Mol Biol Int. 2014: 852748, doi:10.1155/2014/852748, 9 pages
541. Ishihara, J., Otani, T., Inoue, M., Iwasaki, M., Sasazuki, S., Tsugane, S. and for the Japan Public Health Center based prospective study group. 2007. Low intake of vitamin B-6 is associated with increased risk of colorectal cancer in Japanese men. The Journal of Nutrition. 137(7):1808-1814
542. Islam, M. A., Sooro, M. A. and Zhang, P. 2018. Autophagic regulation of p62 is critical for cancer therapy. Int J Mol Sci. 19(5): 1405, doi: 10.3390/ijms19051405, 15 pages.
543. Isoda, K., Young, J. L., Zirlik, A., MacFarlane, L. A., Tsuboi, N., Gerdes, N., Schonbeck, U. and Libby, P. 2006. Metformin inhibits proinflammatory responses and nuclear factor-kappaB in human vascular wall cells. Arterioscler Thromb Vasc Biol. 26(3): 611-7
544. Izzo, A. A. and Camilleri, M. 2008. Emerging role of cannabinoids in gastrointestinal and liver diseases: basic and clinical aspects. Gut. 57(8): 1140-55
545. Jabbour, A. M., Heraud, J. E., Daunt, C. P., Kauffmann, T., Sandow, J., O'Reilly, L. A., Callus, B. A., Lopez, A., Strasser, A., Vaux, D. L. and Ekert, P. G. 2009. Puma indirectly activates Bax to cause apoptosis in the absence of Bid or Bim. Cell Death Differ. 16(4): 555-63
546. Jacobs, E. J., Connell, C. J., McCullough, M. L., Chao, A., Jonas, C. R., Rodriguez, C., Calle, E. E. and Thun, M. J. 2002. Vitamin C, vitamin E and mutivitgamin supplement use and stomach cancer mortality in the cancer prevention study II cohort. Cancer Epidemiol Biomarkers Prev. 11(1): 35-41 PMID:11815399
547. Jacobs, E. J., Connell, C. J., Patel, A. V., Chao, A., Rodriguez, C., Seymour, J., McCullough, M. L., Calle, E. E. and Thun, M. J. 2001. Vitamin C and vitamin E supplement use and colorectal

cancer mortality in a large American cancer society cohort. Cancer Epidemiology, Biomarkers and Prevention. 10(1):17-23, PMID:11205484

548. Jacobs, E. J., Connell, C. J., Patel, A. V., Chao, A., Rodriguez, C., Seymour, J., McCullough, M. L., Calle, E. E. and Thun, M. J. 2001. Vitamin C and vitamin E supplement use and colorectal cancer mortality in a large American cancer society cohort. Cancer Epidemiology, Biomarkers and Prevention. 10(1):17-23, PMID:11205484

549. Jacobs, E. T., Alberts, D. S., Benuzillo, J., Hollis, B. W., Thompson, P. A. and Martinez, M. E. 2007. Serum 25 (OH) D levels, dietary intake of vitamin D and colorectal adenoma recurrence. The Journal of Steroid Biochemistry and Molecular Biology. 103(3-5): 752-756

550. Jacobsen, J., Grankvist, K., Rasmuson, T., Bergh, A., Landberg, G. and Ljunberg, B. 2004. Expression of vascular endothelial growth factor protein in human renal cell carcinoma. BJU International. 93(3): 297-302

551. Jamali, N., Sorenson, C. and Sheibani, N. 2014. Vitamin D attenuates proangiogenic properties of pericytes through increased production of VEGF. The FASEB Journal. 28: 679.1 (Abstract of presentation, Supl 1).

552. Jamshidzadeh, A., Aminlari, M. and Rasekh, H. 2001. Rhodanese and arginase activity in normal and cancerous tissue of human breast, oesophagus, stomach and lung. Ira Med. 4(2): 88-89

553. Janeway, A. C., Travers, P. Jr. and Walport, M. 2001. The immune system in health and disease. Immunobiology, 7th Edition. ISBN: 9780815341239, 928 pages

554. Jang, S. H., Lim, J. W. and Kim, H. 2009. B-carotene inhibits *Helicobacter pylori*-induced expression of inducible nitric oxide synthase and cyclooxygenase-2 in human gastric epithelial AGS cells. Journal of Physiology and Pharmacology. 60(Suppl 7): 131-137

555. Jani, J. P., Finn, R. S., Campbell, M., Coleman, K. G., Connell, R. D., Currier, N., Emerson, E. O., Floyd, E., Harriman, S.,

Kath, J. C., Morris, J., Moyer, J. D., Pustilnik, L. R., Rafidi, K., Ralston, S., Rossi, A. M., Steyn, S. J., Wagner, L., Winter, S. M. and Bhattacharya, S. K. 2007. Discovery and pharmacologic characterization of CP-724714, a selective ErbB2 tyrosine kinase inhibitor. Cancer Res. 67(20): 9887-93

556. Janku, F., Yap, T. A. and Meric-Bernstam, F. 2018. Targeting the PI3K pathway in cancer: are we making headway? Nat Rev Clin Oncol. 15(5): 273-291

557. Jayasena, C. S., Ohyama, T., Segil, N. and Groves, A. K. 2008. Notch signaling augments the canonical Wnt pathway to specify the size of the otic placode. Development. 135(13): 2251-2261

558. Jee, S. H., Ohrr, H., Sull, J. W., Yun, J. E. and Ji, M., Samet, J. M. 2005. Fasting serum glucose level and cancer risk in Korean men and women. JAMA. 293(2): 194-202

559. Jeffery, E. H. and Stewart, K. E. 2004. Upregulation of quinine reductase by glucosinolate hydrolysis products from dietary broccoli. Methods Enzymol. 382: 457-69, doi: 10.1016/ S0076-6879(04)82025-1

560. Jelic, D., Lower-Nedza, D. A., Brantner, H. A., Blazekovic, B., Bian, B., Yang, J., Brajsa, K. and Vladimir-Knezevic, S. 2016. Baicalin and baicalein inhibits Src tyrosine kinase and production of IL-6. Journal of Chemistry. Article ID 2510621, 6 pages, http://dx.doi.org/10.1155/2016/2510621

561. Jeon, H., Kim, H., Choi, D., Kim, D., Park, S. Y., Kim, Y. J., Kim, Y. M. and Jung, Y. 2007. Quercetin activates an angiogenic pathway, hypoxia inducible factor (HIF)-1-vascular endothelial growth factor, by inhibiting HIF-prolyl hydroxylase: a structural analysis of quercetin for inhibiting HIF-prolyl hydroxylase. Mol Pharmacol. 71(6):1676-84

562. Jeong, Y. J., Lee, J. Y., Han, H. J., Park, Y. S., Hwang, W. K. and Sohn, D. U. 2014. The inhibitory effect of PIK-75 on inflammatory mediator response induced by hydrogen peroxide in feline esophageal epithelial cells. Mediators of Inflamm. 2014: 178049, doi: 10.1155/2014/178049

563. Jeong, Y., Li, H., Kim, S. Y., Yun, H., Baek, K. J., Kwon, N. S., Myung, S. C. and Kim, D. 2011. Indol-3-carbinol inhibits

prostate cancer cell migration via degredation of β-catenin. Oncology Research. 19: 237-243, doi: 10.3727/096504011X12 970940207922

564. Jeronimo, M. S., Barros, A. P., Moritai, V. E. Z., Alves, E. O., de Souza, N. L. B., de Almeida, R. M., Nobrega, Y. K. M., Neto, F. F. C., Amorin, R., Borin, M. F. and Bocca, A. L. 2016. Oral or topical administration of L-arginine changes the expression of TGF and iNOS and results in early wounds healing. Acta Cirurgica Brasileira. 31(9): 586-596

565. Ji, C., Xu, Y., Han, F., Sun, D., Zhang, H., Li, X., Yao, X. and Wang, H. 2017. Quercetin alleviates thermal and cold hyperalgesia in a rat neuropathic pain model by inhibiting Toll-like receptor signaling. Biomedicine & Pharmacotherapy. 94: 652-658, https:// doi.org/10.1016/j.biopha.2017.07.145

566. Ji, G., Zhang, Y., Yang, Q., Cheng, S., Hao, J., Zhao, X. and Jiang, Z. 2012. Genistein suppresses LPS-induced inflammatory response through inhibiting NF-kB following AMP kinase activation in RAW 264.7 macrophages. Plos One. 7(12): e53101, doi: 10.1371 / journal.pone. 00533101, 7 pages.

567. Ji, X., Wang, Z., Geamanu, A., Sarkar, F. H. and Gupta, S. V. 2011. Inhibition of cell growth and induction of apoptosis in non-small cell lung cancer cells by delta-tocotrienol is associated with notch-1 down regulation. Journal of Cellular Biochemistry. 112(10): 2773-2783

568. Ji, Y., Wang, Z., Wang, H., Zhang, C., Zhang, Y., Zhao, M., Chen, Y., Meng, X. and Xu, D. 2012. Ascorbic acid protects against cadmium-induced endoplasmic reticulum stress and germ cell apoptosis in testes. Reproductive Toxicology. 34(3): 357-363

569. Jiagang, D., Wang, H., Liu, Y., Li, C., Hao, E., Du, Z., Bao, C., Lv, J. and Wang, Y. 2012. Anti-atherosclerotic effects mediated by the combination of Probucol and amygdalin in apolipoprotein E-knockout mice fed with a high fat diet. Journal of Animal and Veterinary Advances. 11(1): 20-25, doi: 10.3923/ javaa.2012.20.25

570. Jiang, B. and Liu, L. 2009. PI3K/PTEN signaling in angiogenesis and tumorigenesis. Adv Cancer Res. 102:19-65, doi:10.1016/S0065-230X(09)02002-8

571. Jiang, H., Wang, J. and Zhao, W. 2013. Cox-2 in non-small cell lung cancer: A meta-analysis. Clinica Chimica Acta. 419: 26-32, https: //doi.org/10.1016/j.cca.2013.01.012

572. Jiang, J. and Hui, C. C. 2008. Hedgehog signaling in development and cancer. Dev Cell. 15(6): 801-12

573. Jiang, J., Kang, B. T., Shim, W. D., Oh, H. N., Kim, J. T. and Lee, H. K. 2013. Indole-3-carbinol inhibits LPS-induced inflammatory response by blocking TRIF-dependent signaling pathway in macrophages. Food and Chemical Toxicology. 57: 256-261, http://dx.doi.org/10.1016/j.fct.2013.03.040

574. Jiao, Y. B., Rui, Y. C., Yang, P. Y., Li, T. J. and Qiu, Y. 2007. Effects of *Ginkgo biloba* extract on expressions of IL-1beta, TNF-alpha, and IL-10 in U937 from cells. Yao Xue Xue Bao. 42(9): 930-4

575. Jimeno, A., Weiss, G., Miller Jr, W. H., Gettinger, S., Eigl, B. J. C., Chang, A. L. S., Dunbar, J., Devens, S., Faia, K., Skliris, G., Kutok, J., Lewis, K. D., Tibes, R., Shafman, W. H., Ross, R. W. and Rudin, C. M. 2013. Phase 1 study of the Hedgehog pathway inhibitor IPI-926 in adult patients with solid tumors. Clin Cancer Res. 19(10): 2766-2774

576. Jin, E. Y., Lim, S., Kim, S., Park, Y., Jang, J. K., Chung, M., Park, H., Shim, K. and Choi, Y. J. 2011. Optimization of various extraction methods for quercetin from onion skin using response surface methodology. Food Sci Biothechnol. 20(6): 1727-1733

577. Jin, G., Zhang, F., Chan, K. M., Xavier Wong, H. L., Liu, B., Cheah, K. S., Liu, X., Mauch, C., Liu, D. and Zhou, Z. 2011. MT1-MMP cleaves Dll1 to negatively regulate Notch signaling to maintain normal B-cell development. EMBO J. 30(11): 2281-93

578. Jin, H., Gong, W., Zhang, C. and Wang, S. 2013. Epigallocatechin gallate inhibits the proliferation of colorectal cancer cells by regulating Notch signaling. Onco Targets Ther. 6: 145-53, doi: 10.2147/OTT.S40914

579. Jin, U. H., Suh, S.J., Chang, H. W., Son, J. K., Lee, S. H., Son, K. H., Chang, Y. C. and Kim, C. H. 2008. Tanshinone IIA from *Salvia miltiorrhiza Bunge* inhibits human aortic smooth muscle cell migration and MMP-9 activity through AKT signaling pathway. J Cell Biochme. 104(1): 15-26, doi:10.1002/jcb.21599
580. Jin, Y., Zhang, W., Wang, H., Zhang, Z., Chu, C., Liu, X. and Zou, Q. 2016. EGFR/HER2 inhibitors effectively reduce the malignant potential of MDR breast cancer evoked by -gp substrates in vitro and in vivo. Oncol Rep. 35(2): 771-8
581. Jing, Y., Ma, N., Fan, T., Wang, C., Bu, X., Jiang, G., Li, R., Gao, L., Li, D., Wu, M. and Wei, L. 2016. Tumor necrosis factor-alpha promotes tumor growth by inducing vascular endothelial growth factor. Cancer Invest. 29(7): 485-93
582. Jo, G. H., Kim, G., Kim, W., Park, K. Y. and Choi, Y. H. 2014. Sulforaphane induces apoptosis in T24 human urinary bladder cancer cells through a reactive oxygen species-mediated mitochondrial pathway: The involvement of endoplasmic reticulum stress and the Nrf2 signaling pathway. International Journal of Oncology. 45(4): 1497-1506
583. Joshi, S., Wei, J. and Bishopric, N. H. 2016. A cardiac myocyte-restricted Lin28/Let7 regulatory axis promotes hypoxia-mediated apoptosis by inducing the Akt signaling suppressor PIK3IP1. Biochim Biophys Acta. 1862(2): 240-251
584. Juengel, E., Thomas, A., Rutz, J., Makarevic, J., Tsaur, I., Nelson, K., Haferkamp, A. and Blaheta, R. A. 2016. Amygdalin inhibits the growth of renal cell carcinoma cells in vitro. International Journal of Molecular Medicine. 37:526-532, doi:10.3892/ijmm.2015.2439
585. Juengel, E., Thomas, A., Rutz, J., Makarevic, J., Tsaur, I., Nelson, K., Haferkamp, A. and Blaheta, R. 2015. Amygdalin inhibits the growth of renal cell carcinoma cell in vitro. International Journal of Molecular Medicine. 37(2): 526-532
586. Jung, W. K., Choi, I., Lee, D. Y., Yea, S. S., Choi, Y. H., Kim, M. M., Park, S. G., Seo, S. K., Lee, S. W., Lee, C. M., Park, Y. M. and Choi, I. W. 2008. Cafeic acid phenethyl ester protects mice from lethal endotoxin shock and inhibits lipopolysacharide-indced

cyclooxygenase-2 and inducible nitric oxide synthase expression in RAW 264.7 macrophages via the p38/ERK and NF-kappaB pathways. Int J Biochem Cell Biol. 40(11): 2572-82

587. Jurzak, M. and Adamczyk, K. 2013. Influence of genistein on C-Jun, C-Fos and Fos-B ofAP-1 subunits expression in skin keratinocytes, fibroblasts and keloid fibroblasts cultured in vitro. Acta Poloniae Pharmaceutica-Drug Research. 70(2): 205-213

588. Kaizu, T., Tamaki, T., Tanaka, M., Uchida, Y., Tsuchihashi, S., Kawamura, A. and Kakita, A. 2003. Preconditioning with tin—protoporphyrin IX attenuates ischemia/reperfusion injury in the rat kidney. Kidney International. 63: 1393-1403, doi: 10.1046/j.1523-1755.2003.00882.x

589. Kamakura, S., Oishi, K., Yoshimatsu, T., Nakafuku, M., Masuyama, N. and Gotoh, Y. 2004. Hes binding to STAT3 mediates crosstalk between Notch and JAK-STAT signaling. Nat Cell Biol. 6(6): 547-54

590. Kamangar, F., Qiao, Y., Yu, B., Sun, X., Abnet, C. C., Fan, J., Mark, D. S., Zhao, P., Dawsey, M. S. and Taylor, R. P. 2006. Lung cancer chemoprevention: a randomized, double-blind trial in Linxian, China. Cancer Epidemiology, Biomarkers and Prevention. 15(8): 1562-1564

591. Kan, S., Wang, J. and Sun, G. 2018. Sulforaphane regulates apoptosis-and proliferation-related signaling pathways and synergizes with cisplatin to suppress human ovarian cancer. International Journal of Molecular Medicine. 42(5): 2447-2458

592. Kang, K. S., Wang, P., Yamabe, N., Fukui, M., Jay, T. and Zhu, B. T. 2010. Docosahexaenoic acid induces apoptosis in MCF-7 cells in vitro and in vivo via reactive oxygen species formation and caspase 8 activation. Plos One. 5(4): 310296, 13 pages, doi: 10.1371/journal.pone.0010296

593. Kang, K., Shu, X. L., Zhong, J. X. and Yu, T. T. 2014. Effect of L-arginine on immune function: a meta-analysis. Asia Pac J Clin Nutr. 23(3): 351-9

594. Kang, M., Park, S., Kim, Y., Lee, E., Antika, L. D., Kim, D. Y., Choi, Y. and Kang, Y. 2017. Chrysin ameliorates podocyte injury

and slit diaphragm protein loss via inhibition of the PERK-eIF2α-ATF-CHOP pathway in diabetic mice. Acta Pharmacol Sin. 38(8): 1129-1140

595. Kanlaya, R., Khamchun, S., Kapincharanon, C. and Thongboonkerd, V. 2016. Protective effect of epigallocatechin-3-gallate (EGCG) via Nrf2 pathway against oxalate-induced epithelial mesencyhymal transition (EMT) of renal tubular cells. Scientific Reports. 13 pages, doi: 10.1038/srep30233, 6: 30233

596. Kannan, S. and Zweidler-McKay, P. A. 2015. A novel Notch/ Nrf2 mechanism mediates reductive stress in acute myeloblastic leukemia (AML): A therapeutic strategy to overcome chemoresistance. Blood. 126(23): 4834-4834

597. Kanno, S., Kitajima, Y., Kakuta, M., Osanai, Y., Kurauchi, K., Ujibe, M. and Ishikawa, M. 2008. Costunolide-induced apoptosis is caused by receptor-mediated pathway and inhibition of telomerase activity in NALM-6 cells. Biol Pharm Bull. 31(5): 1024-8

598. Karapanagioti, A. G., Nasiri-Ansari, N., Angelousi, A., Kalotychou, V., Papavasillou, A. G. and Kassi, E. 2018. Vitamin D abolishes the dexamethasone-induced apoptosis in acute myeloid leukemia cells via regulation of Notch signaling. Endocrine Abstracts. 56: P673, doi: 10.1530/endoabs. 56.P673

599. Karhadkar, S. S., Bova, G. S., Abdallah, N., Dhara, S., Gardner, D., Maitra, A., Isaacs, J. T., Berman, D. M. and Beachy, P. A. 2004. Hedgehog signaling in prostate regeneration, neoplasia and metastasis. Nature. 431(7009): 707-12

600. Karimi, G., Vahabzadeh, M., Lari, P., Rashedinia, M. and Moshiri, M. 2011. 'Silymarin', a promising pharmacological agent for treatment of diseases. Iran J Basic Med. Sci. 14(4): 308-317

601. Karioti, A., Carta, F. and Supuran, T. C. 2016. An update on natural products with carbonic anhydrase inhibitory activity. Current Pharmaceutical Design. 22(12): 1570-91

602. Kasai, H., Fukada, S., Yamaizumi, Z., Sugie, S. and Mori, H. 2000. Action of chlorogenic acid in vegetables and fruits as an inhibitor of 8-hydroxydeoxyguanosine formation in vitro and in a rat carcinogenesis model. Food Chem Toxicol. 38(5): 467-71

603. Kasai, Y., Maegawa, M., Yamamoto, S., Kamada, M., Yasui, T., Uemura, H., Kobayashi, A., Kaneyama, M., Tani, A., Matsui, S., Kuwahara, A., Matsuzaki, T., Furumoto, H. and Irahara, M. 2011. Effects of raloxifene on the production of cytokines in stimulated whole blood in ex vivo and in vivo studies. J Med Invest. 58(1-2): 110-7

604. Kasaoka, T., Nishiyama, H., Okada, M. and Nakajima, M. 2008: Matrix metalloproteinase inhibitor, MM1270 (GCS27023A) inhibited hematogenic metastasis of B_{16} melanoma cells in both experimental and spontaneous metastasis models. Clin Exp Metastasis. 25(7): 827-34

605. Katiyar, S. K. 2015. Hsp90 inhibitor can inhibit UV carcinogenesis. Journal of Investigative Dermatology. 135: 945-947, doi: 10.1038/jid.2014.504

606. Kaur, G., Shukla, A., Sivakumar, S. and Verma, S. 2015. Soft structure formation and cancer cell transport mechanisms of a folic acid-dipeptide conjugate. Journal of PeptideScience. 21: 248-255, doi: 10.1002/psc.2742

607. Kaur, H., He, B., Zhang, C., Rodriguez, E., Hage, D. S. and Moreau, R. 2018. Piperine potentiates curcumin-mediated repression of mTORC1 signaling: implications for the inhibition of protein synthesis and TNFα signaling. The Journal of Nutritional Biochemistry. 57: 276-286, https://doi.org/10.1016/j.jnutbio.2018.04.010

608. Kaushal, G. P., Kaushal, V., Hong, X. and Shah, S. V. 2001. Role and regulation of activation of caspases in cisplatin-induced injury to renal tubular epithelial cells. Kidney International. 60: 1726-1736, doi: 10.1046/j.1523-1755.2001.00026

609. Kaushik, S., Shyam, H., Sharma, R. and Balapure, A. K. 2018. Dietary isoflavone daidzein synergizes centchroman action via induction of apoptosis and inhibition of PI3K/Akt pathway in MCF-7/MDA MB-231 humann breast cancer cells. Phytomedicine. 40: 116-124, doi: 10.1016 / j.phymed.2018.01.007

610. Kawagoe, J., Ohmichi, M., Takahashi, T., Ohshima, C., Mabuchi, S., Takahashi, K., Igarashi, H., Mori-Abe, A., Saitoh, M., Du, B., Ohta, T., Kimura, A., Kyo, S., Inoue, M. and Kurachi, H.

2003. Raloxifene inhibits estrogen-induced up-regulation of telomerase activity in a human breast cancer cell line. J Biol Chem. 278(44): 43363-72

611. Kawamura, T., Liu, D., Towle, M. J., Kageyama, R., Tsukahara, N. and Wakabayashi, T. 2003. Anti-angiogenesis effects of borrelidin are mediated through distinct pathways: threonyl-tRNA synthetase and caspases are independently involved in suppression of proliferation and infection of apoptosis in endothelial cells. The Journal of Antibiotics. 56(8): 709-15

612. Kayashima, T., Tanaka, K., Okazaki, Y., Matsubara, K., Yanaka, N. and Kato, N. 2011. Consumption of vitamin B_6 reduces colonic damage and protein expression of HSP70 and HO-1, the anti-tumor targets, in rats exposed to 1,2-dimethylhydrazine. Oncol Lett. 2(6): 1243-1246

613. Ke, J., Long, X., Liu, Y., Zhang, Y. F., Li, J., Fang, W. and Meng, Q. G. 2007. Role of NF-kappaB in TNF-alpha-induced COX-2 expression in synovial fibroblasts from human TMJ. J Dent Res. 86(4): 363-7

614. Kearney, J., Giovannucci, E., Rimm, E. B., Ascherio, A., Stampfer, M. J., Colditz, G. A., Wing, A., Kampman, E. and Willett, W. C. 1996. Calcium, vitamin D and dairy foods and the occurrence of colon cancer in men. American Journal of Epidemiology. 143(9): 907-917

615. Kelley, R. M., Logsdon, D. and Fishel, L. M. 2014. Targeting DNA repair pathways for cancer treatment: what's new?. Future Oncol. 10(7): 1215-1237

616. Kempuraj, D., Huang, M., Kandere-Grzybowska, K., Basu, S., Boucher, W., Letourneau, R., Athanassiou, A. and Theoharides, T. C. 2003. Azelastine inhibits secretion of IL-6, TNF-alpha and IL-8 as well as NF-kappaB activation and intracellular calcium ion levels in normal human mast cells. Int Arch Allergy Immunol. 132(3): 231-9

617. Kennedy, B. K. and Lamming, D. W. 2016. The mechanistic target of rapamycin: the grand conductor of metabolism and aging. Cell Metabolism. 23: 990-1003, http://dx.doi.org/10.1016/j. cmet .2016.05.009

618. Keshavan, P., Schwemberger, S. J., Smith, D. L. H., Babcock, G. F. and Zucker, S. D. 2004. Unconjugated bilirubin induces apoptosis in colon cancer cells by triggering mitochondrial depolarization. Int J Cancer. 112(3): 433-445

619. Keum, Y. S., Yu, S., Chang, P. P., Yuan, X., Kim, J. H., Xu, C., Han, J., Agarwal, A. and Kong, A. N. 2006. Mechanism of action of sulphoraphane: Inhibition of p38 mitogen-activated protein kinase isoforms contributing to the induction of antioxidant response element-mediated heme oxygenase-1 in human hepatoma HepG2 cells. Cancer Res. 66(17): 8804-13

620. Key, J. T., Appleby, N. P., Allen, E. N., Travis, C. R., Roddam, W. A., Jenab, M., Egevad, L., Tjonneland, A., Johnsen, F. N., Overvad, K., Linseisen, J., Rohrmann, S., Boeing, H., Pischon, T., Psaltopoulou, T., Trichopoulou, A., Trichopoulos, D., Palli, D., Vineis, P., Tumino, R., Berrino, F., Kiemeney, L., Bueno-de-Mesquita, B. H., Quiros, R. J., Gonzales, A. C., Martinez, C., Larranaga, N., Chirlaque, D. M., Ardanaz, E., Stattin, P., Hallmans, G., Khaw, K., Bingham, S., Slimani, N., Ferrari, P., Rinaldi, S. and Riboli, E. 2007. Plasma carotenoids, retinol, and tocopherols and the risk of prostate cancer in the European prospective investigation into cancer and nutrition study. Am J Clin Nutr. 86(3): 672-681

621. Key, T. J., Appleby, P. N., Masset, G., Brunner, J. E., Cade, J. E., Greenwood, D. C., Stephen, A. M., Kuh, D., Bhaniani, A., Powell, N. and Khaw, K. 2012. Vitamins, minerals, essential fatty acids and colorectal cancer risk in the United Kingdom Dietary Cohort Consortium. Int J Cancer. 131(3): E320-E325

622. Khaliullina, H., Bilgin, M., Sampaio, J. L., Shevchenko, A. and Eaton, S. 2015. Endocannabinoids are conserved inhibitors of the Hedgehog pathway. Proceedings of the National Academy of Sciences of the United States of America. 112(11): 3415-3420

623. Khan, F., Ali, A. and Ali, R. 2005. Enhanced recognition of hdroxyl radical modified plasmid DNA by circulating cancer antibodies. J Exp Clin Cancer Res. 24(2): 289-96

624. Khan, N. M., Haseeb, A., Ansari, M. Y. and Haggi, T. M. 2017. A wogonin-rich-fraction of Scutellaria baicalensis root extract

exerts chondroprotective effects by suppressing IL-1B-induced activation of AP-1 in human OA chondrocytes. Sci Rep. 7: 43789, doi: 10.1038/srep43789, 14 pages

625. Khanna, A. K. 2009. Enhanced susceptibility of cyclin kinase inhibitor p21 knockout mice to high fat diet induced atherosclerosis. J Biomed Sci. 16(1): 66, doi: 10.1186/1423-0127-16-66, 12 pages

626. Khaodhiar, L., Ricciotti, H. A., Li, L., Pan, W., Schickel, M., Zhou, J. and Blackburn, G. L. 2008. Daidzein-rich isoflavone aglycones are potentially effective in reducing hot flashes in menopausal women. Menopause. 15(1): 125-132, PMID: 1825146

627. Kharebava, G., Rashid, M. A., Lee, J., Sarkar, S., Kevala, K. and Kim, H. 2015. N-dososahexaenoylethanolamine regulates Hedgehog signaling and promotes growth of cortical axons. Biol Open. 4(12): 1660-1670

628. Kheirelseid, H. A. E., Miller, N., Chang, K. H., Curran, C., Hennessey, E., Sheehan, M. and Kerin, J. M. 2013. Mismatch repair protein expression in colorectal cancer. J Gastrointest Oncol. 4(4): 397-408

629. Kikuchi, N., Ohmori, K., Shimazu, T., Nakaya, N., Kuriyama, S., Nishino, Y., Tsubono, Y. and Tsuji, I. 2006. No association between green tea and prostate cancer risk in Japanese men: the Ohsaki cohort study. Br J Cancer. 95(3): 371-373

630. Kilkkinen, A., Knekt, P., Heliövaara, M., Rissanen, H., Marniemi, J., Hakulinen, T. and Aromaa, A. 2008. Vitamin D status and the risk of lung cancer: A cohort study in Finland. Cancer Epidemiology, Biomarkers and Prevention. 17(11): 3274-3278

631. Kim, D. H.and Jin, Y. H. 2001. Intestinal bacterial beta-glucuronidase activity of patients with colon cancer. Arch Pharm Res. 24(6):564-7.

632. Kim, A., Nam, Y. J., Shin, Y. K., Lee, M. S., Sohn, D. S. and Lee, C. S. 2017. Rotundarpene inhibits TNF-α-induced activation of the Akt, mTOR and NF-kB pathways, and the JNK and p38 associated with production of reactive oxygen species. Molecular and Cellular Biochemistry. 434 (Issues 1-2): 113-125, https://doi.org/10.1007/s11010-017-3041-x

633. Kim, B. and Hong, S. H. 2011. Sequential caspase-2 and caspase-8 activation is essential for saikosaponin a-induced apoptosis of human colon carcinoma cell lines. Apoptosis. 16(2): 184-97

634. Kim, B., Seo, H., Ku, J., Kim, G., Jeon, C. Y., Park, J. H., Jang, B., Park, S., Shin, Y. and Ko, S. 2013. Silibinin inhibits the production of pro-inflammatory cytokines through inhibition of NF-kB signaling pathway in HMC-1 human mast cells. Inflamm Res. 62: 941-950, doi: 10.1007/s00011-013-0640-1

635. Kim, D. H., Jung, W., Kim, M. E., Lee, H., Youn, H., Seon, J. K., Lee, H. and Lee, J. S. 2014. Genistein inhibits pro-inflammatory cytokines in human mast cell activation through the inhibition of ERK pathway. International Journal of Molecular Medicine. 34(6): 1669-1674

636. Kim, D. S., Kim, J. H., Lee, G. H., Kim, H. T., Lim, J. M., Chae, S. W., Chae, H. J. and Kim, H. R. 2010. P38 mitogen-activated protein kinase is involved in endoplasmic reticulum stress-induced cell death and autophagy in human gingival fibroblasts. Biol Pharm Bull. 33(4): 545-9

637. Kim, E. J., Kim, J., Lee, M. Y., Sudhanva, M. S., Devakumar, S. and Jeon, Y. J. 2014. Silymarin inhibits cytokine-stimulated pancreatic beta cells by blocking the ERK1/2 pathway. Biomol Ther (Seoul): 22(4): 282-287

638. Kim, G., Jang, M. S., Son, Y. M., Seo, M. J., Si, Y. S., Seung, H. H., Jung, I. D., Park, Y., Jung, H. J. and Yun, C. 2013. Curcumin inhibits CD4+ T cell activation, but augments CD69 expression and TGF-β1-mediated generation of regulatory T cells at late phase. PlosOne. 8(Issue 4): e62300, https://doi.org/10.1371/journal.pone.0062300, 12 pages

639. Kim, H. G., Hwang, Y. P., Han, E. H., Choi, J. H., Kwon, K., Chung, Y. C., Jeong, M. H., Jeong, T. C., Kang, W. and Jeong, H. G. 2012. The coffee diterpene kahweol inhibits metastasis by modulating expressions of MMPs and VEGF via STAT3 inactivation. Food Chemistry. 133(4): 1521-1529

640. Kim, H. N., Kim, H., Kong, J. M., Bae, S., Kim, Y. S., Lee, N., Cho, B. J., Lee, S. K., Kim, H., Hwang, Y., Kang, J. S. and Lee,

W. J. 2011. Vitamin C down-regulates VEGF production in B16F10 murine melanoma cells via the suppression of p42/44 MAPK activation. Journal of Cellular Biochemistry. 112(3): 894-901

641. Kim, H., Lee, M., Jeong, Y., Ro, H., Kim, D., Shin, Y., Kim, J., Hwang, K., Choi, J., Bahn, M., Lee, J., Lee, S. H., Bae, Y., Lee, J., Choi, J., Kim, N., Yeo, C. and Kim, C. 2017. Ottogi inhibits Wnt/β-catenin signaling by regulating cell membrane trafficking by Frizzled 8. Scientific Reports. 7(1): 13278, doi: 10.1038/s41598-13429-6, 13 pages

642. Kim, H., Lee, S., Um, J., Oh, W. K., Kim, D., Kang, C. and Kim, S. 2015. Sensitization of multidrug-resistant human cancer cells to Hsp90 inhibitors by down-regulation of SIRT1. Oncotarget. 6(34): 36202-36218

643. Kim, H., Moon, J. Y., Ahn, K. S. and Cho, S. K. 2013. Quercetin induces mitochondrial mediated apoptosis and protective autophagy in human glioblastoma U373MG cells. Oxidative Medicine and Cellular Longevity. 2013: 596496, doi: 115/2013/596496, 10 pages.

644. Kim, J. O., Hong, H. S., Oh, S. H., Kim, J. O., Hong, H. S., Oh, S. H., Kim, T. G., Min, T. K., Oh, D. and Kim, N. K. 2011. Association between VEGF polymorphisms and homocysteine levels in patients with ischemic stroke and silent brain infection. Stroke. 42:2393-2402, http: // doi. Org / 10.1161 / STROKEEAHA. 110. 607739

645. Kim, J., Tang, J. Y., Gong, R., Kim, J., Lee, J. J., Clemons, K. V., Chong, C. R., Chang, K. S., Fereshteh, M., Gardner, D., Reya, T., Liu, J.O., Epstein, E. H., Stevens, D. A. and Beachy, P. A. 2010. Itraconazole, a commonly used antifungal that inhibits Hedgehog pathway activity and cancer growth. Cancer Cell. 17(4): 388-99

646. Kim, J.E., Jin, D.H., Lee, S.D., Hong, S.W., Shin, J.S., Lee, S.K., Jung, D.J., Kang, J.S. and Lee, W.J. 2008. Vitamin C inhibits p53-induced replicative senescence through suppression of ROS production and p38 MAPK activity. Int J Mol Med. 22(5):651-5

647. Kim, K., Song, Y. and Lim, H. 2005. Amygdalin extract from *Armeniacae* semen induces apoptosis in human COLO201 colon cancer cells. Korean Journal of Oriental Medicine. 26(4): 108-121

648. Kim, N., Lee, M., Park, S., Choi, J., Oh, M. and Kim, I. 2007. Auranofin blocks interleukin-6 signaling by inhibiting phosphorylation of JAK1 and STAT3. Immunology. 122(4): 607-614

649. Kim, S. A. and Choi, H. C. 2012. Metformin inhibits inflammatory response via AMPK-PTEN pathway in vascular smooth muscle cells. Biochem Biophys Res Commun. 425(4): 866-72

650. Kim, S. H., Baek, M. S., Yoon, D. S., Park, J. S., Yoon, B. W., Oh, B. S., Park,J. and Kim, H. J. 2014. Vitamin D inhibits expression and activity of matrix metalloproteinase in human lung fibroblasts (HFL-1) cells. Tuberc Respir Dis. 77(2): 73-80

651. Kim, S. H., Kim, M. H., Jeong, M., Hwang, Y. S., Lim, S. H., Shin, B. A., Ahn, B. W. and Jung, Y. D. 2004. EGCG blocks tumor promoter-induced MMP-9 expression via suppression of MAPK and AP-1 activation in human gastric AGS cells. Anticancer Research. 24(2B): 747-754

652. Kim, S. H., Park, J. G., Sung, G., Yang, S., Yang, W. S., Kim, E., Kim, J. H., Ha, V. T., Kim, H. G., Yi, Y., Kim, J. H., Baek, K., Sung, N. Y., Lee, M., Kim, J. and Cho, J. Y. 2015. Kaempferol, a dietary flavonoid, ameliorates acute inflammatory and nociceptive symptoms in gastritis, pancreatitis, and abdominal pain. Molecular Nutrition. 59(7): 1400-1405

653. Kim, S. J., Park, Y. S., Paik, H. D. and Chang, H. I. 2011. Effect of anthocyanins on expression of matrixmetalloproteinase-2 in naproxen-induced gastric ulcers. Br J Nutr. 106(12): 1792-801

654. Kim, S., Huang, H., Zhao, M., Zhang, X., Zhang, A., Semenov, M., MacDonald, B. T., Zhang, X., Abreu, T. G., Peng, L. and He, X. 2013. Wnt stabilization of β-catenin reveals principles for morphogen receptor-scaffold assemblies. Science. 340(6134): 867-870

655. Kim, S., Kim, D. H., Jung, W. H. and Koo, J. S. 2013. Expression of glutamine metabolism-related proteins according to molecular subtype of breast cancer. Endocr Relat Cancer. 20(3): 339-48
656. Kim, S., Roszik, J., Grimm, E. A. and Ekmekcioglu, S. 2018. Impact of L-arginine metabolism on immune response and anticancer immunotherapy. Front Oncol. 8: 67, doi: 10.3389/ fonc.2018.00067, 5 pages
657. Kim, Y. 2003. Role of folate in colon cancer development and progression. J Nutr. 133(11): 37315-37395
658. Kim, Y. and Lee, J. 2014. Anti-inflammatory activity of capsaicin and dihydrocapsaicin through heme oxygenase-1 induction in Raw264.7 macrophages. Journal of Food Biocehmsitry. 38(4): 381-387
659. Kim, Y. J., Park, J., Lee, E. J. and Yenari, A. M. 2017. Nox inhibitors-A promising avenue for ischemic stroke. Exp Neurobiol. 26(4): 195-205
660. Kim, Y., Kim, C., Joe, Y., Chung, H. T., Ha, T. Y. and Yu, R. 2018. Alpha-induced muscle atrophy by upregulation of heme oxygenase-1. Journal of Medicinal Food. 21(6): 551-559
661. Kim, Y., Lee, H., Lim, J. Y., Jung, C., Yoo, S. and Kim, Y. 2014. B-carottene inhibits neuroblastoma cell invasion and metastasis in vitro and in vivo by decreasing level of hypoxia-inducible factor-1α. The Journal of Nutritional Biochemistry. 25(6): 655-664
662. Kim, Y., Seo, J. H. and Kim, H. 2011. B-carotene and lutein inhibit hydrogen peroxide-induced activation of NF-kB and IL-8 expression in gastric epithelial AGS cells. J Nutr Sci. Vitaminol. 57(3): 216-223
663. Kim-Park, W. K., Allam, E. S., Palasuk, J., Kowalik, M., Park, K. K. and Windsor, J. L. 2016. Green tea catechin inhibits the activity and neutrophil release of matrix metalloproteinase-9. Journal of Traditional and Complementary Medicine. 6(4): 343-346
664. King, C. E., Cuatrecasas, M., Castells, A., Sepulveda, A. R., Lee, J. S. and Rustgi, A. K. 2011. LIN28B promotes colon cancer progression and metastasis. Cancer Res. 71(12): 4260-8

665. King, J. C., Lu, Q., Li, G., Moro, A., Takahashi, H., Chen, M., Go, V. L., Reber, H. A., Eibl, G. and Hines, O. J. 2012. Evidence for activation of mutated p53 by apigenin in human pancreatic cancer. Biochim Biophys Acta. 1823(2):593-604

666. King, M. D., Alleyne, C. H. Jr. and Dhandapani, K. M. 2013. TNF-alpha receptor antagonist, R-7050, improves neurological outcomes following intracerebral hemorrhage in mice. Neurosci Lett. 542: 92-6, doi: 10.1016/j.neulet. 2013.02.051

667. Kioka, N., Hosokawa, N., Komano, T., Hirayoshi, K., Nagata, K. and Ueda, K. 1992. Quercetin, a bioflavonoid, inhibits the increase of human multidrug resistance gene (MDR1) expression caused by arsenite. 301(3): 307-309

668. Kiraly, A. J., Soliman, E., Jenkins, A. and Van Dross, R.T. 2016. Apigenin inhibits COX-2, PGE2, and EP1 and also initiates terminal differentiation in the epidermis of tumor bearing mice. Prostaglandins Leukot Essent Fatty Acids. 104:44-53. doi: 10.1016/j.plefa.2015.11.006.

669. Kirkegaard, T., Yde, C. W., Kveiborg, M. and Lykkesfeldt, A. E. 2014. The broad-spectrum metalloproteinase inhibitor BB-94 inhibits growth, HER3 and Erk activation in fulvestrant-resistant breast cancer cell lines. Int J Oncol. 45(1): 393-400, doi: 10.3892/ijo.2014.2434

670. Kirouac, D. C., Du, J., Lahdenranta, J., Onsum, D. M., Nielsen, U. B., Schoeberl, B. and McDonagh, F. C. 2016. HER2+ cancer cell dependence on PI3K vs. MAPK signaling axes is determined by expression of EGFR, ERBB3 and CDKN1B. PlosOne Comput Biol. 12(4):e1004827, doi: 10.1371/journal. pcbl.1004827, 23 pages

671. Kirsh, A. V., Mayne, T. S., Peters, U., Chatterjee, N., Leitzmann, F. M., Dixon, B. L., Urban, A. D., Crawford, D. E. and Hayes, B. R. 2006. A prospective study of lycopene and tomato product intake and risk of prostate cancer. Cancer Epidemiol Biomarkers Prev. 15(1): 92-8 DOI:10.1158/1055-9965.EPI-05-0563

672. Kitamura, H. and Motohashi, H. 2018. Nrf2 addiction in cancer cells. Cancer Sci. 109(4): 900-911

673. Kitamura, T., Asai, N., Enomoto, A., Maeda, K., Kato, T., Ishida, M., Jiang, P., Watanabe, T., Usukura, J., Kondo, T., Costantini, F., Murohara, T. and Takahashi, M. 2008. Regulation of VEGF-mediated angiogenesis by the Akt/PKB substrate Girdin. Nature Cell Biology. 10(3):329-37

674. Kivela, A. M., Kansanen, E., Jyrkkanen, H., Nurmi, T., Yla-Herttuala, S. and Levonen, A. 2008. Enterolactone induces heme oxygenase-1 expression through nuclear factor-E2-related factor 2 activation in endothelial cells. The Journal of Nutrition. 138(7): 1263-1268

675. Klein, E. A., Thompson, M. I., Tangen, M. C., Crowley, J. J., Lucia, S. M., Goodman, P. J., Minasian, M. L., Ford, G. L., Parnes, L. H., Gaziano, M. J., Karp, D. D., Lieber, M. M., Walther, J. P., Klotz, L., Parsons, K. J., Chin, L. J., Darke, K. A., Lippman, M. S., Goodman, E. G., Meyskens, L. F. and Baker, H. L. 2011. Vitamin E and the risk of prostate cancer. The selenium and vitamin E cancer prevention trial (Select). JAMA. 306(4): 1549-1556

676. Klein-Soyer, C., Ceraline, J., Orvain, C., de la Salle, C., Bergerat, J. P. and Cazenave, J. P. 1997. Angiogenesis inhibitor SR 25989 upregulates thrombospondin-1 expression in human vascular endothelial cells and foreskin fibroblasts. Biol Cell. 89(4): 295-307

677. Knekt, P., Aromaa, A., Maatela, J., Aaran, R., Nikkari, T., Hakama, M., Hakulinen, T., Peto, R. and Teppo, L. 1991. Vitamin E and cancer prevention. Am J Clin Nutr. 53(1): 2835-2865, doi: 10.1093/ajcn/53.1.283S.

678. Knekt, P., Kumpulainen, J., Jarvinen, R., Rissanen, H., Heliovaara, M., Reunanen, A., Hakulinen, T. and Aromaa, A. 2002. Flavonoid intake and risk of chronic diseases. Am J Clin Nutr. 76(3): 560-568

679. Knight, A. Z., Gonzales, B., Feldman, E. M., Zunder, R. E., Goldenberg, D. D., Williams, O., Loewith, R., Stokoe, D., Balla, A., Toth, B., Balla, T., Weiss, A. W., Williams, L. R. and Shokat, M. K. 2006. A pharmacological Map of the PI3-K family defines a role for p110α in insulin signaling. Cell. 125(4): 733-747

680. Knight, D. S., Adams, D. N., Burgess, L. J., Chaudhari, A. M., Daray, M. G., Donatelli, C. A., Luengo, J. I., Newlander, K. A., Parrish, C. A., Ridgers, L. H., Sarpung, M. A., Schmidt, S. J., Van Aller, G. S., Carson, J. D., Diamond, M. A., Elkins, P. A., Gardiner, C. M., Garver, E., Gilbert, S. A., Gontarek, R. R., Jackson, J. R., Kershner, K. L., Luo, L., Raha, K., Sherk, C. S., Sung, C. M., Sutton, D., Tummino, P. J., Wegrzyn, R. J., Auger, K. R and Dharak, D. 2010. Discovery of GSK2126458, a highly potent inhibitor of PI3K and the mammalian target of rapamycin. ACS Med Chem Lett. 1(1): 39-43, doi: 10.1021/ml900028r

681. Kobori, M., Takahashi, Y., Sakurai, M., Akimoto, Y., Tsushida, T., Oike, H. and Ippoushi, K. 2016. Quercetin suppresses immune cell accumulation and improves mitochondrial gene expression in adipose tissue of diet-induced obese mice. Mol Nutr Food Res. 60(2): 300-312

682. Koeffler, H. P., Lowe, L. and Golde, D. W. 1980. Amygdalin (Laetrile): effect on clonogenic cells from human myeloid leukemia cell lines and normal human marrow. Cancer Treat Rep. 64(1): 105-9, PMID:6929726

683. Kogame, A., Tagawa, Y., Shibata, S., Tojo, H., Miyamoto, M., Tohyama, K., Kondo, T., Prakash, S., Shyu, W. C. and Asahi, S. 2013. Pharmacokinetic and pharmacodynamic modeling of hedgehog inhibitor TAK-441 for the inhibition of Gli1 messenger RNA expression and antitumor efficacy in xenografted tumor model mice. Drug Metab Dispos. 41(4): 727-34

684. Kohyama, T., Takizawa, H., Kawasaki, S., Akiyama, N., Sato, M. and Ito, K. 1999. Fourteen-member macrolides inhibit interleukin-8 release by human eosinophils from atopic donors. Antimicrob Agent Chemother. 43(4): 907-911

685. Kokenyesi, R. and Bernfeld, M. 1994. Core protein structure and sequence determine the site and presence of heparin sulfate and chondroitin sulfate on syndecan-1. The Journal of Biological Chemistry. 269(16): 12304-12309

686. Kolterud, A. and Toftgard, R. 2007. Strategies for Hedgehog inhibition and its potential role in cancer treatment. Drug Discovery Today. Therapeutic Strategies. 4(4): 229-235

687. Komarova, T. V., Kosorukov, V. S., Frolova, O. Y., Petrunia, I. V., Skrypnik, K. A., Gleba, Y. Y. and Dorokhov, Y. L. 2011. Plant-made trastuzumab (Herceptin) inhibits Her2/Neut cell proliferation and retards tumor growth. PlosOne. 6(3): e17541, doi: 1371/journal.pone.0017541, 7 pages

688. Kondapaka, S. B., Zarnowski, M., Yver, D. R., Sausville, E. A. and Cushman, S. W. 2004. 7-hydroxystaurosporine (UCN-01) inhibition of Akt Thr308 but not Ser473 phosphorylation: a basis for decreased insulin-stimulated glucose transport. Clin Cancer Res. 10(21): 7192-8

689. Konings, E. J. M., Goldbohm, R. A., Brants, H. A. M., Saris, W. H. M. and van den Brandt, P. A. 2002. Intake of dietary folate vitamers and risk of colorectal carcinoma. Cancer. 95(7):1421-1433.

690. Koo, B. K., van Es, J. H., van den Born, M. and Clevers, H. 2015. Porcupine inhibitor suppresses paracrine Ent-driven growth of Rnf43; Znrf3-mutant neoplasia. Proc Natl Acad Sci USA. 112(24): 7548-50

691. Koppenol, W. H., Bounds, P. L. and Dang, C. V. 2011. Otto Warburg's contributions to current concepts of cancer metabolism. Nat Rev Cancer. 11(5): 325-337

692. Kosaka, A., Yan, H., Ohashi, S., Gotah, Y., Sato, A., Tsutsui, H., Kaisho, T., Toda, T. and Tsuji, N. M. 2012. *Lactococcus lactis subsp.cremoris* FC triggers IFN-Ɣ production from NK and T cells via IL-12 and IL-18. International Immunopharmacology. 14(4): 729-733

693. Kothari, P., Pestana, R., Mesraoua, R., Elchali, R., Khan, K. M., Dannenberg, A. J. and Falcone, D. J. 2014. IL-6-mediated induction of matrix metalloproteinase-9 is modulated by JAK-dependent IL-10 expression in macrophages. J Immunol. 192(1):349-57, doi: 10.4049/jimmunol.1301906

694. Koul, K. H., Pal, M. and Koul, S. 2013. Role of p38 MAP kinase signal transductionin solid tumors. Genes Cancer. 4(9-10): 342-359

695. Krebs, T. E. and Beard, H. H. 1950. The Unitarian or trophoblastic thesis of cancer. Medical Record. 163(7): 149-174

696. Kremer, J. C., Prudner, B. C., Lange, S. E. S., Michel, L. S., Held, J. M., van Tine, B. A., Brashears, C. B., Radyk, M. D., Redlich, N., Tzeng, S., Kami, K., Shelton, L., Li, A., Morgan, Z., Bomalaski, J. S., Tsukamoto, T., McConathy, J., Michel, L. S., Held, J. M. and van Tine, B. A. 2017. Arginine deprivation inhibits the Warburg effect and upregulates glutamine anaplerosis and serine biosynthesis in ASS1-deficient cancers. Cell Reports. 18(4): 991-1004

697. Kretschmer, N., Rinner, B., Stuendl, N., Kaltenegger, H., Wolf, E., Kunert, O., Boechzelt, H., Leithner, A., Bauer, R. and Lohberger, B. 2012. Effect of costunolide and dehydrococtus lactone on cell cycle, apoptosis, and ABC transporter expression in human soft tissue sarcoma cells. Planta Med. 78(16): 1749-56

698. Krige, D., Needham, L. A., Bawden, L., Flores, N., Farmer, H., Miles, L. E. C., Stone, E., Callaghan, J., Chandler, S., Clark, V. L., Kirwin-Jones, P., Legris, V., Owen, J., Patel, T., Wood, S., Box, G., Laber, D., Odedra, R., Wright, A., Wood, M., Eccles, S. A., Bone, E. A., Ayscough, A. and Drummond, A. H. 2008. CHR-2797: An antiproliferative aminopeptidase inhibitor that leads to amino acid deprivation in human leukemic cells. The Journal of Cancer Research. 68: 6669, doi: 10.1158/0008-5472. CAN-07-6627

699. Krishnamoorthy, G., Selvakumar, K., Venkataraman, P., Elumalai, P. and Arunakaran, J. 2013. Lycopene supplementation prevents reactive oxygen species mediated apoptosis in Sertoli cells of adult albino rats exposed to polychlorinated biphenyls. Interdiscip Toxicol. 6(2): 83-92

700. Krone, C. A. and Ely, J. T. 2005. Controlling hypergyciemia as an adjunct to cancer therapy. Integr Cancer Ther. 4(1): 25-31, doi: 10.1177/1534735404274167

701. Krop, I., Demuth, T., Guthrie, T., Wen, P. Y., Mason, W. P., Chinnaiyan, P., Butowski, N., Groves, M. D., Kesari, S., Freedman, S. J., Blackman, S., Watters, J., Loboda, A., Podtelezhnikov, A., Beckman, R. and LoRusso, P. 2012. Phase 1 pharmacologic and pharmacodynamic study of the gamma secretase (Notch) inhibitor MK-0752 in adult patients with

advanced solid tumors. Journal of Clinical Oncology. 30(19): 2307-13

702. Krupkova, O., Sekiguchi, M., Klasen, J., Hausmann, O., Konno, S., Ferguson, S. J. and Wuertz-Kozak, K. 2014. Epigallocatechin 3-gallate suppresses interleukin-1B-induced inflammatory responses in intervertebral disc cells in vitro and reduces radiculopathic pain in rats. European cells and Materials. 28: 372-386, doi: 10.22203/eCM.v028a26

703. Krusch, M., Salih, J., Schlicke, M., Baessler, T., Kampa, K. M., Mayer, F. and Salih, H. R. 2009. The kinase inhibitors sunitinib and sorafenib differentially affect NK cell antitumor reactivity in vitro. J Immunol. 183(12): 8286-94

704. Ku, H.C., Tsuei, Y.W., Kao, C.C., Weng, J.T., Shih, L.J., Chang, H.H., Liu, C.W., Tsai, S.W., Kuo, Y.C. and Kao, Y.H. Green tea (-)-epigallocatechin gallate suppresses IGF-I and IGF-II stimulation of 3T3-L1 adipocyte glucose uptake via the glucose transporter 4, but not glucose transporter 1 pathway. Gen Comp Endocrinol. 199:46-55. doi: 10.1016/j.ygcen.2014.01.008

705. Kubo, A., Block, G., Quesenberry, CP. Jr., Buffler, P. and Corley DA. 2009. Effects of dietary fiber, fats, and meat intakes on the risk of Barrett's esophagus. Nutr Cancer. 61(5):607-16

706. Kumar, K. K., Priyanka, L., Gnananath, K., Babu, P. R. and Sugatha, S. 2015. Pharmacokinetic drug interactions between apigenin, rutin and paclitaxel mediated by P-glycoprotein in rats. Eur J Drug Metab Pharmacokinet. 40(3): 267-76

707. Kumazoe, M., Takai, M., Hiroi, S., Takeuchi, C., Yamanouchi, M., Najiri, T., Onda, H., Bae, J., Huang, Y., Takamatsu, K., Yamashita, S., Yamada, S., Kangawa, K., Takahashi, T., Tanaka, H. and Tachibana, H. 2017. PDE3 inhibitor and EGCG combination treatment suppress cancer stem cell properties in pancreatic ductal adenocarcinoma. Scientific Reports. 7: 1917, doi: 10.1038/s41598-017.02162-9

708. Kunicka, T. and Soucek, P. 2014. Importance of ABCC1 for cancer therapy and prognosis. Drug Metab Rev. 46(3): 325-42

709. Kurahashi, N., Sasazuki, S., Iwasaki, M., Inoue, M. and Tsugane, S. 2008. Green tea consumption and prostate cancer

risk in Japanese men: A prospective study. Am J Epidemiol. 167(1): 71-77, doi:10.1093/aje/kwm249

710. Kurebayashi, J., Otsuki, T., Kurosumi, M., Soga, S., Akinaga, S. and Sonoo, H. 2001. A radicicol derivative, KF58333, inhibits expression of hypoxia-inducible factor-1alpha and vascular endothelial growth factor, angiogenesis and growth of human breast cancer xenografts. Jpn J Cancer Res. 92(12): 1342-51

711. Kushi, L. H., Fee, R. M., Sellers, T. A., Zheng, W. and Folsom, A. R. 1996. Intake of vitamins A, C and E and postmenopausal breast cancer. The Iowa women's health study. American Journal of Epidemiology. 144(2):165-169

712. Kwon, G. T., Jung, J. I., Song, H. R., Woo, E. Y., Jun, J. G., Kim, J. K., Her, S. and Park, J. H. 2012. Piceatannol inhibits migration and invasion of prostate cancer cells: possible mediation by decreased interleukin-6 signaling. J Nutr Biochem. 23(3): 228-38

713. Kwon, H. Y., Hong, S. P., Hahn, D. H. and Kim, J. H. 2003. Apoptosis induction of Persicae semen extract in human promyelocytic leukemia (HL-60) cells. Arch Pharm Res. 26(2): 157-61

714. Kwon, S., Choi, H., Kang, Y. and Park, K. 2017. Depigmenting effect of resveratrol is dependent on Foxo3a activation without SIRT1 activation. Int J Mol Sci. 18(6): 1213, doi: 10.3390 / ijms18061213, 11 pages

715. La Vecchia, C., Negri, E., Pelucchi, C. and Franceschi, S. 2002. Dietary folate and colorectal cancer. Int J Canver. 102(5): 545-547

716. Labudzynskyi, D., Shymanskyy, I. and Veliky, S. M. 2016. Role of vitamin D_3 in regulation of interleukin-6 and osteopontin expression in liver of diabetic mice. European Review for Medical and Pharmacological Sources. 20(13): 2916-1919

717. Lagente, V., Manoury, B., Nenan, S., Le Quement, C., Martin-Chouly, C. and Boichot, E. 2005. Role of matrix metalloproteinases in the development of airway inflammation and remodeling. Brazilian Journal of Medical and Biological Research. 38(10): 1521-1530

718. Lahav, M., Levite, M., Bassani, L., Lang, A., Fidder, H., Tal, R., Bar-meir, S., Mayer, L. and Chowers, Y. 2002. Lidocaine inhibits secretion of IL-8 and IL-1β and stimulates secretion of IL-1 receptor antagonist by epithelial cells. Clin Exp Immunol. 127(2): 226-233

719. Lai, C. J., Bao, R., Tao, X., Wang, J., Atoyan, R., Qu, H., Wang, D. G., Yin, L., Samson, M., Forrester, J., Zifcak, B., Xu, G. X., DellaRocca, S., Zhai, H. X., Cai, X., Munger, W. E., Keegan., Pepicelli, C. V. and Qian, C. 2010. CUDC-101, a multitargeted inhibitor of histone deacetylase, epidermal growth factor receptor 2, exerts potent anticancer activity. Cancer Res. 70(9): 3647-56

720. Lai, Y. G., Weinstein, J. S., Albanes, D., Taylor, R. P., Virtamo, J., McGlynn, A. K. and Freedman, D. N. 2014. Association of serum α-tocopherol, β-carotene and retinol with liver cancer incidence and chronic liver disease mortality. British Journal of Cancer. 111: 2163-2171, doi: 10.1038/bjc.2014.365

721. Lam, K. T., Rotunno, M., Lubin, J. H., Wacholder, S., Consonni, D., Pesatori, C. A., Bertazzi, A. P., Chanock, J. S., Burdette, L., Goldstein, M. A., Tucker, A. M., Caporaso, E. N., Subar, F. A. and Landi, T. M. 2010. Dietary quercetin, quercetin-gene interaction, metabolic gene expression in lung tissue and lung cancer risk. Carcinogenesis. 31(4): 634-642

722. Lam, L., Hu, X., Aktary, Z., Andrews, D. W. and Pasdar, M. 2009. Tamoxifen and ICI 182,780 increase Bcl-2 levels and inhibit growth of breast carcinoma cells by modulating PI3K/ AKT, ERK and IGF-1R pathways independent of ERalpha. Breast Cancer Res Treat. 118(3): 605-21

723. Lampiasi, N., Fodera, D., D'Alessandro, N., Cusimano, A., Azzolina, A., Tripodo, C., Florena, A. M., Minervini, M. I., Notarbartolo, M., Montalto, G. and Cervello, M. 2006. The selective cyclooxygenase-1 inhibitor SC-560 suppresses cell proliferation and induces apoptosis in human hepatocellular carcinoma cells. Int J Mol Med. 17(2): 245-52

724. Landgren, R. C., Hussey, D. H., Samuels, M. L. and Leary, W. V. 1973. A randomized study comparing irradiation alone

to irradiation plus procarbazine in inoperable bronchogenic carcinoma. Radiology. 108(2): 403-406

725. Landor, S. K., Mutvei, A. P., Mamaeva, V., Jin, S., Busk, M., Borra, R., Grönroos, T. J., Krongvist, P., Lendahl, U. and Sahlgren, C. M. 2011. Hypo-and hyperactivated Notch signaling induce a glycolytic switch through distinct mechanism. Proc Ntl Acad Sci USA. 108(46): 18814-9

726. Lappano, R., Sebastiani,. A. Cirillo, F., Rigiracciolo, D. C., Galli, C. R., Curcio, R., Malaguarnera, R., Belfiore., Cappello, A. R. and Maggiolini, M. 2017. The lauric acid-activated signaling prompts apoptosis in cancer cells. Cell Death Discov. 3: 1706, doi: 10.1038/cddiscovery.2017.633.

727. Lappas, C. M. and Lappas, N. T. 2012. D-Limonene modulates T lymphocyte activity and viability. Cellular Immunology. 279(1): 30-41, https:/doi.org/10.1016/j.cellimm.2012.09.002

728. Larsson, D. E., Wickstrom, M., Hassan, S., Oberg, K. and Granberg, D. 2010. The cytotoxic agents NSC-95397, brefeldin A, bortezomib and sanguinarine induce apoptosis in neuroendocrine tumors in vitro. Anticancer Research. 30(1): 149-156, PMID:20150630

729. Larsson, S. C., Giovannucci, E. and Wolk, A. 2005. Vitamin B_6 intake, alcohol consumption and colorectal cancer: A longitudinal population based cohort of women. Gastroenterology. 128(7):1830-1837

730. Laster, W. R. and Schabel, F. M. 1975. Experimental studies of the antitumor activity of amygdalin MF(NSC-15780) alone and in combination with β-glucosidase (NSC-128056). Cancer Chemother Rep. 59(5): 951-965

731. Laurella, L. C., Cerny, N., Bivona, A. E., Alberti, A. S., Giberti, G., Malchiodi, E. L., Martino, V. S., Catalan, C. A., Alonso, M. R., Cazorla, S. I. and Sülsen, V. P. 2017. Assesment of sesquiterpene lactones isolated from *Mikania* plants species for their potential efficacy against *Trypanosoma cruzi* and *Leishmania* sp. Plos Negl Trop Dis. 11(9): e0005929, https://doi.org/10.1371/journal.pntd.0005929, 16 pages

732. Lauricella, M., Emanuele, S., D'Anneo, A., Calvaruso, G., Vassallo, B., Portanova, C. D., Vento, R. and Tesoriere, G. 2006. JNK and HepG2 cells via FasL/caspase-8 and mitochondria-dependent pathways. Apoptolsis. 11: 607-625, doi: 10.1007/s10495-006-4689-y

733. Le Marchand, L., White, K. K., Nomura, A. M. Y., Wilkens, L. R., Selhub, J. S., Tiirikainen, M., Goodman, H. T., Murphy, S. P., Henderson, B. E. and Kolonel, L. N. 2009. Plasma levels of B vitamins and colorectal cancer risk:the multiethnic cohort study. 18(8):2195-2201

734. Lea, M. A. and Koch, M. R. 1979. Effects of cyanate, thiocyanate, and amygdalin on metabolite uptake in normal and neoplastic tissues of the rat. J Natl Cancer Inst. 63(5): 1279-83

735. Leach, D. R., Krumel, M. F. and Allison, J. P. 1996. Enhancement of antitumor immunity by CTLA-4 blockade. Science. 271(5256): 1734-6

736. Leal, F. L., Bueno, A. C., Gomes, C. D., Abduch, R., de Castro, M. and Antonini, S. R. 2015. Inhibition of the Tcf/beta-catenin complex increases apoptosis and impairs adrenocortical tumor cell proliferation and adrenal steroidogenesis. Oncotarget. 6(40): 43016-4302

737. Lecleire, S., Hassan, A., Marion-Letellier, R., Antonietti, M., Savoye, G., Böle-Feysot, C., Lerebours, E., Ducrotte, P., Decholette, P. and Coeffier, M. 2008. Combined glutamine amd arginine decrease proinflammatory cytokine production by biopsies from Crohn's patients in association with changes in nuclear factor–kB and p38 mitogen-activated protein kinase pathways. The Journal of Nutrition. 138(12): 2481-2486

738. Lederle, W., Depner, S., Schnur, S., Obermueller, E., Catone, N., Fusenig, N. E. and Mueller, M. M. 2011. IL-6 promotes malignant growth of skin SCCs by regulating a network of autocrine and paracrine cytokines. Int J Cancer. 128(12): 2803-14

739. Lednicer, D. 2002. Tracing the origin of COX-2 inhibitors' structures. Curr Med Chem. 9(15): 1457-61

740. Lee, A. S. 2007. GRP78 induction in cancer: Therapeutic and prognostic implications. Cancer Research. 67(8): 3496-3499

741. Lee, B., Jung, J. H. and Kim, H. S. 2012. Assessment of red onion on antioxidant activity in rat. Food Chem Toxicol. 50(11): 3912-9

742. Lee, C. M., Lee, J., Nam, M. J. and Park, S. 2018. Indole-3-carbinol induces apoptosis in human osteosarcoma MG-63 and U2OS cells. BioMed Research International. Volume 2018, Article ID 7970618, 13 pages, https://doi.org/10.1155/2018/7970618

743. Lee, D. E., Chung, M. Y., Lim, T. G., Huh, W. B., Lee, H. J. and Lee, K. W. 2013. Quercetin suppresses intracellular ROS formation, MMP activation, and cell motility in human fibrosarcoma cells. J Food Sci. 78(9): H1464-9

744. Lee, D. H. and Lee, C. S. 2016. Flavonoid myricetin inhibits TNF-α-stimulated production of inflammatory mediators by suppressing the Akt, mTOR and NF-kB pathways in human keratinocytes. European Journal of Pharmacology. 784: 164-172, doi: 10.1016 / j.ejphar. 2016.05.025

745. Lee, D. H. and Lee, Y. J. 2008. Quercetin suppresses hypoxia-induced accumulation of hypoxia-inducible factor-1alpha (HIF-1alpha) through inhibiting protein synthesis. J Cell Biochem. 105(2): 546-53

746. Lee, D. H., Park, J. S., Lee, Y. S., Sung, S. H., Lee, Y. and Bae, S. H. 2017. The hypertension drug, verapamil, activates Nrf2 by promoting p62-dependent autophagic Keap1 degradation and prevents acetaminophen-induced cytotoxicity. BMB Rep. 50(2): 91-96

747. Lee, D. Y., Lin, X., Paskaleva, E. E., Liu, Y., Puttamadappa, S. S., Thornber, C., Drake, J. R., Habulin, M., Shektman, A. and Canki, M. 2009. Palmitic acid is a novel CD4 fusion inhibitor that blocks HIV entry and infection. AIDS Res Hum Retroviruses. 25(12): 1231-41

748. Lee, E., Choi, M., Lee, Y., Ku, J., Kim, K., Choi, J. and Lim, S. 2006. Alpha-tocopheryl succinate, in contrast to alpha-tocopherol and alpha-tocopheryl acetate, inhibits prostaglandin E2 production in human lung epithelail cells. Carcinogenesis. 27(11): 2308-2315

749. Lee, E., Enomoto, R., Koshiba, C. and Hirano, H. 2009. Inhibition of P-glycoprotein by wogonin is involved with the potentiation of etoposide-induced apoptosis in cancer cells. Ann. N. Y. Acad. Sci. 1171:132-136, doi: 10.1111/j.1749-6632.2009.04722.x

750. Lee, G. R. 2018. The balance of Th17 versus Treg cells in autoimmunity. Int J Mol Sci. 19(3): 730, doi: 10.3390/ijms19030730, 14 pages

751. Lee, H. H., Lee, S., Shin, Y. S., Cho, M., Kang, H. and Cho, H. 2016. Anti-cancer effect of quercetin in xenograft models with EBV-associated human gastric carcinoma. Molecules. 21:1286, doi:10.3390/molecules21101286

752. Lee, H. J., So, J., DeCastro, A., Smolarek, A., Paul, S., Maehr, H., Uskokovic, M. and Suh, N. 2010. Gemini vitamin D analog suppresses ErbB2-positive mammary tumor growth via inhibition of ErbB2/Akt/Erk signaling. J Steroid Biochem Mol Biol. 121(1-2): 408-412

753. Lee, H. J., Wu, Q., Li, H., Bae, G., Kim, A. K. and Ryu, J. 2016. A sesquiterpene lactone from *Siegesbeckia glabrescens* suppresses Hedgehog/Gli-mediated transcription in pancreatic cancer cells. Oncol Lett. 12(4): 2912-2917

754. Lee, H. S., Lee, C. H., Tsai, H. C. and Salter, D. M. 2009. Inhibition of cyclooxygenase 2 expression by diallyl sulfide on joint inflammation induced by urate crystal and IL-1B. Osteoarthritis and Cartilage. 17(1): 91-99

755. Lee, I. T., Lee, C. W., Tung, W. H., Wang, S. W., Lin, C. C., Shu, J. C. and Yang, C. M. 2010. Cooperation of TLR2with MyD88, PI3K, and Pacl in lipoteichhoic acid-induced cPLA2/COX-2-dependent airway inflammatory responses. Am J Pathol. 176(4): 1671-84

756. Lee, I. T., Lin, C. C., Wu, Y. C. and Yang, C. M. 2010. TNF-alpha induces matrix metalloproteinase-9 expression in A549 cells:role of TNFR1/TRAF2/PKCalpha-dependent signaling pathways. J Cell Physiol. 224(2):454-64

757. Lee, J. Y., Lee, T. H., Shin, W., Chae, J., Choi, J., Kim, S. H., Lim, H., Heo, T. W., Park, K. Y., Lee, J. Y., Ryu, E. S., Son, Y. J., Lee, U. J. and Heo, Y. 2016. Structural basis of checkpoint

blockade by monoclonal antibodies in cancer immunotherapy. Nat Commun. 7:13354, doi: 10.1038/ncomms13354, 10 pages

758. Lee, K. H., Jeong, J. and Yoo, C. G. 2013. Long-term incubation with proteasome inhibitors (PIs) induces Ikβα degradation via the lysosomal pathway in an IkB kinase (IKK)-dependent and IKK-independent manner. J Biol Chem. 288(45): 32777-86

759. Lee, K., Chae, S. W., Xia, Y., Kim, N. H., Kim, H. J., Rhie, S. and Lee, H. J. 2014. Effect of coumarin derivative-mediated inhibition of P-glycoprotein on oral bioavailability and therapeutic efficacy of paclitaxel. European Journal of Pharmacology. 723:381-388, http://dx.doi.org/10.1016/ j.ejphar.2013.11.002

760. Lee, M. H. and Moon, A. 2016. Amygdalin regulates apoptosis and adhesion in Hs578T triple-negative breast cancer cells. Biomol Ther (Seoul). 24(1): 62-66

761. Lee, M. K., Lee, W. K., Jung, S. K., Lee, J. E., Heo, Y., Bode, A. M., Lubet, A. R., Lee, H. J. and Dong, Z. 2010. Kaempferol inhibits UVB-induced COX-2 expression by suppressing Src kinase activity. Biochem Pharmacol. 80(12): 2042-2049

762. Lee, S. A., Kim, H. J., Chang, K. C., Baek, J. C., Park, J. K., Shin, J. K., Choi, W.J., Lee, J. H. and Paik, W. Y. 2009. DHA and EPA down-regulate COX-2 expression through suppression of NF-kB activity in LPS-treated human umbilical vein endothelial cells. Korean J Physiol Pharmacol. 13(4): 301-307

763. Lee, S. H., Nam, H. J., Kang, H. J., Kwon, H. W. and Lim, Y. C. 2013. Epigallocatechin-3-gallate attenuates head and neck cancer stem cell traits through suppression of Notch pathway. European Journal of Cancer. 49(15): 3210-3218

764. Lee, S., Choi, E. J., Jin, C. and Kim, D. H. 2005. Activation of PI3K/Akt pathway by PTEN reduction and PIK3CAmRNA amplification contributes to cisplatin resistance in an ovarian cancer cell line. Gynecol Oncol. 97(1): 26-34, doi:10.1016/j. ygyno.2004.11.051

765. Lee, S., Lim, M., Kim, M., Yu, C., Yun, Y., Ahn, J. and Song, J. 2012. An effective strategy for increasing the radiosensitivity of human lung cancer cells by blocking Nrf2-dependent antioxidant responses. Free Radical Biology and Medicine. 53(4): 807-816

766. Lee, S., Ro, H., In, H. J., Choi, J., Kim, M., Lee, J., Hong, S. and Lee, S. U. 2018. Fisetin inhibits TNF-α/NF-kB-induced IL-8 expression by targeting PKCδ in human airway epithelial cells. Cytokine. 108: 247-254, https://doi.org/10.1016/j.cyto.2018.01.004

767. Lee, S., Son, Y., Kook, S., Choi, K. and Lee, J. 2011. Ascorbic acid increases the activity and synthesis of tyrosinnase in B16F10 cells through activation of p38 mitogen-activated protein kinase. Archives of Dermatological Research. 303(9): 669-678

768. Lee, T. Y., Chang, C. C., Lu, W. J., Yen, K. H., Geraldine, P., Li, J. Y. and Sheu, J. R. 2017. Honokiol as a specific collogen receptor glycoprotein VI antagonist on human platelets: Functional ex vivo and in vitro studies. Sci Rep. 7: 40002, doi:10.1038/srep40002, 13 pages.

769. Lee, W. S., Lee, E. G., Sung, M. S. and Yoo, W. H. 2014. Kaempferol inhibits IL-1B-stimulated, RANKL-mediated osteoclastogenesis via downregulation of MAPKs, c-Fos, and NFATc1. Inflammation. 37(4): 1221-30

770. Lee, W., Hsiao, M., Chang, J., Yang, S., Tseng, T., Cheng, C. and Chow, J. 2015. Quercetin induces mitochondrial-derived apoptosis via reactive oxygen species-mediated ERK activation in HL-60 leukemia cells and xenograft. Archives of Toxicology. 89(7): 1103-1117

771. Lee, Y. and Lee, S. 2011. Sulforaphane induces antioxidative and antiproliferative responses generating reactive oxygen species in human bronchial epithelial BEAS-2B cells. J Korean Med Sci. 26(11): 1474-1482

772. Lee, Y., Hwang, J., Kwon, D. Y., Surh, Y. and Park, J. O. 2010. Induction of apoptosis by quercetin is mediated through AMPKα1/ASK1/p38 pathway. Cancer Letters. 292(2): 228-236

773. Lee, Y., Noh, E., Han, J., Kim, J., Hwang, B., Kim, B., Lee, S., Jung, S. H., Chung, E. Y. and Kim, J. 2013. Sulforaphane controls TPA-induced MMP-9 expression through the NF-kB signaling pathway, but not AP-1, in MCF-7 breast cancer cells. BMB Rep. 46(4): 201-206

774. Leitner, J. M., Mayr, F. B., Firbas, C., Spiel, A. O., Steinlechner, B., Novellini, R. and Jilma, B. 2007. Reparixin, a specific interleukin-8 inhibitor, has no effects on inflammation during endotoxemia. Int J Immunopathol Pharmacol. 20(1): 25-36, doi:10.1177/039463200702000104

775. Leitner, J. M., Mayr, F. B., Firbas, C., Spiel, A. O., Steinlechner, B., Novellini, R. and Jilma, B. 2007. Reparixin, a specific interleukin-8 inhibitor, has no effects on inflammation during endotoxemia. Int J Immunopathol Pharmacol. 20(1): 25-36, doi:10.1177/039463200702000104

776. Lenhard, M., Tsvilina, A., Schumacher, L., Kupka, M., Ditsch, N., Mayr, D., Friese, K. and Jeschke, U. 2012. Human chorionic gonadotropin and its relation to grade, stage and patient survival in ovarian cancer. BMC Cancer. 12: 2, doi: 10.1186/1471-2407-12-2, 8 pages

777. Lenton, K. J., Sane, A. T., Therriault, H., Cantin, A. M., Payette, H., Wagner, J. R. 2003. Vitamin C augments lymphocyte glutathione in subjects with ascorbate deficiency. Am J Clin Nutr. 77(1):189-195, doi:10.1093/ajcn/77.1.189

778. Leon-Galicia, I., Diaz-Chavez, J., Garcia-Villa, E., Uribe-Figueroa, L., Hidalgo-Miranda, A., Herrera, L. A., Alvarez-Rios, E., Garcia-Mena, J. and Gariglio, P. 2013. Resveratrol induces downregulation of DNA repair genes in MCF-7 human breast cancer cells. Eur J Cancer Prev. 22(1): 11-20

779. Levy, D. S., Kahana, J. A. and Kumar, R. 2009. Akt inhibitor, GSK 690693, induces growth inhibition nd apoptosis in acute lymphoblastic leukemia cell lines. Blood. 113(8): 1723-9

780. Lewis, J. D., Deren, J. J. and Lichtenstain, G. R. 1999. Cancer risk in patients with inflammatory bowel disease. Gastrointestinal Clin North Am. 28(2): 459-77

781. Leychenko, A., Konorev, E., Jijiwa, M. and Matter, M. L. 2011. Stretch-induced hypertrophy activates NF-kB-mediated VEGF secrfetion in adult cardiomyocites. Plos One. 6(12): e29055, doi: 10.1371/journal.pone.0029055, 9 pages

782. Li W., Zhao, Y., Tao, B. and Zhang Y. 2014. Effects of quercetin on hedgehog signaling in chronic myeloid leukemia KBM7 cells. Chin J Integr Med. 20(10):776-81.

783. Li, B., Cong, M., Zhu, Y., Xiong, Y., Jin, W., Wan, Y., Zhou, Y., Ao, Y. and Wang, H. 2017. Indole-3-carbinol induces apoptosis of hepatic stellate cells through K63 de-ubiquitination of R1P1 in rats. Cellular Physiology and Biochemistry. 41: 1481-1490, https://doi.org/10.1159/000470650

784. Li, C. J., Chang, J. K., Chou, C. H., Wang, G. J.,and Ho, M. L. 2010. The PI3K/Akt/FOXO3a/p27Kip1 signaling contributes to anti-inflammatory drug-suppressed proliferation of human osteoblasts. Biochem Pharmacol. 79(6): 926-37

785. Li, C. Y., Chao, L. K., Wang, S. C., Chang, H. Z., Tsai, M. L., Fang, S. H., Liao, P. C., Ho, C. L., Chen, S. T., Cheng, W. C., Chiang, C. S., Kuo, Y. H., Hua, K. F. and Hsu, I. C. 2011. Honokiol inhibits LPS-induced maturation and inflammatory response of human monocyte-derived dentritic cells. J Cell Physiol. 226(9): 2338-49

786. Li, C., Li, R., Kahl, S. and Elsasser, T. H. 2012. Alpha-tocopherol alters transcription activities that modulates tumor necrosis factor alpha (TNF-α) induced inflammatory response in bovine cells. Gene Regul Syst Bio. 6: 1-14, doi: 10.4137/GRSB.S8303

787. Li, C., Wu, H., Yang, Y., Liu, J. and Chen, Z. 2018. Sesquiterpene lactone 6-0-angeloylphenolin reverses vincristine resistance by inhibiting YB-1 nuclear translocation in colon carcinoma cells. Oncol Lett. 15(6): 9673-9680

788. Li, C., Zang, Y., Sen, M., Leeman-Neill, R. J., Man, D. S., Grandis, J. R. and Johnson, D. E. 2009. Bortezomib up-regulates activated signal transducer and activator of transcription-3 and synergizes with inhibitors of signal transducer and activator of transcription-3 and synergizes with inhibitors of signal transducer and activator of transcription-3 to promote head and neck squamous cell carcinoma cell death. Mol Cancer Ther. 8(8): 2211-20

789. Li, C., Zhou, Y., Peng, X., Du, L., Tian, H., Yang, G., Niu, J. and Wu, W. 2014. Sulforaphane inhibits invasion via activating

ERK1/2 signaling in human glioblastoma U87MG and U373MG cells. PlosOne. 9(2): e90520, doi:10.137/journal.pone.0090520, 12 pages

790. Li, F., Yang, Y., Yang, L., Wang, K., Zhang, X., Zong, Y., Ding, Y., Wang, C., Zhang, L. and Ji, G. 2017. Resveratrol alleviates FFA and CCl4 induced apoptosis in HepG2 levels via restoring endoplasmic reticulum stress. Oncotarget. 8(27): 43799-43809

791. Li, H., Krstin, S., Wang, S. and Wink, M. 2018. Capsaicin and piperine can overcome multidrug resistance in cancer cells to doxorubicin. Molecules. 23(3): 557, doi: 10.3390/ molecules23030557, 11 pages

792. Li, H., Tian, S., Liu, Z., Yu, J. and Yan, J. 2018. Inhibition of cisplatin-resistant tumor cells on activated CD4+ T cells in ovarian cancer and its mechanism. Pharmaceutical Bioprocessing. 6(4): 154-158

793. Li, H., Yuan, Y., Zhang, Y., He, Q., Xu, R., Ge, F. and Wu, C. 2016. Celastrol inhibits IL-1B-induced inflammation in orbital fibroblasts through the suppression of NF-kB activity. Mol Med Rep. 14(3): 299-806

794. Li, J. and Lee, A. S. 2006. Stress induction of GRP78/BIP and its role in cancer. Curr Mol Med. 6(1): 45-54, PMID:16472112

795. Li, J., Li, J., Yue, Y., Hu, Y., Cheng, W., Liu, R., Pan, X. and Zhang, P. 2014. Genistein suppresses tumor necrosis factor α-induced inflammation via modulating reactive oxygen species/Akt/nuclear factor kβ and adenosine monophosphate-activated protein kinase signal pathways in human synoviocyte MH7A cells. Drug Des Devel Ther. 8: 315-323, doi: 10.2147/ DDDT.S52354

796. Li, J., Liu, Y., Zhang, J., Yu, X., Wang, X. and Zhao, L. 2016. Effects of resveratrol on P-glycoprotein and cytochrome P450 3A in vitro and on pharmacokinetics of oral saquinavir in rats. Drug Des Devel Ther. 10: 3699-3706, doi: 10.2147/DDDT. S118723

797. Li, J., Zhu, F., Lubet, R. A., Luca, A. De., Grubbs, C., Ericson, M. E., D'Alessio, A., Normano, N., Dong, Z. and Bode, A. M. 2013. Quercetin-3-methyl ether inhibits lapatinib-sensitive and

resistant breast cancer cell growth by inducing G2/M arrest and apoptosis. Mol Carcinog. 52(2): 134-143

798. Li, L., Khan, M. N., Li, Q., Chen, X., Wei, J., Wang, B., Cheng, J. W., Gordon, J. R. and Li, F. 2015. G31P, CXCR1/2 inhibitor, with cisplatin inhibits the growth of mice hepatocellular Wu, S. J. and Ng, L. T. 2007. Tetrandrine inhibits proinflammatory cytokines, INOS and COX-2 expression in human monocytic cells. Biol Pharm Bull. 30(1): 59-62, doi: 10.3892/or.2014.3659

799. Li, L., Liu, J., Nie, S., Ding, L., Wang, L., Liu, J., Liu, W. and Zhang, T. 2017. Direct inhibition of Keap1-Nrf2 interaction by egg-derived peptides DKK and DDW revealed by molecular docking and fluorescence polarization. RSC Advances. 7: 34963-34971, doi: 10.1039/c7ra04352j

800. Li, M., Zhang, Q., Liu, L., Lu, W., Wei, H., Li, W. R. and Lu, S. 2013. Expression of the mismatch repair gene hMLH1 is enhanced in non-small cell lung cancer with EGFR mutations. Plos One. 8(10): e78500, https://doi.org/10.1371/journal.pone.0078500, 7 pages

801. Li, P., Nijhawan, D., Budihardjo, I., Srinivasula, S. M., Ahmad, M., Alnemri, E. S. and Wang, X. 1997. Cytochrome c and dATP-dependent formation of Apaf-1/caspase-9 complex initiates an apoptotic protease cascade. Cell. 91(4): 479-89

802. Li, T., Kong, A. N., Ma, Z., Liu, H., Liu, P., Xiao, Y., Jiang, X. and Wang, L. 2016. Protein arginine methyltransferase 1 may be involved in pregnane x receptor-activated overexpression of multidrug resistance 1 gene during acquired multidrug resistant. Oncotarget. 7(15): 20236-48

803. Li, T., Zhang, L. and Huo, X. 2018. Inhibitory effects of aesculetin on the proliferation of colon cancer cells by the Wnt/β-catenin signaling pathway. Oncol Lett. 15(5): 7118-7122

804. Li, W., Zhao, Y., Tao, B. and Zhang, Y. 2014. Effects of quercetin on hedgehog signaling on chronic myeloid leukemia KBM7 cells. Chin J Integr Med. 20(10): 776-81

805. Li, X., Kong, L., Li, J., He, H. nad Zhou, Y. 2012. Kaempferol suppresses lipid accumulation in macrophages through the downregulation of cluster of differentiation 36 and the

upregulation of scavenger receptor class B type I and ATP-binding cassette transporters A1 and G1. International Journal of Molecular Medicine. 31(2): 331-338

806. Li, X., Xue, L. and Peng, Q. 2018. Tunicamycin inhibits progression of glioma cells through downregulation of the MEG-3-regulated Wnt-β-catenin signaling pathway. Oncol Lett. 15(6): 8470-8476

807. Li, Y. L., Li, Q. X., Liu, R. J. and Shen, X. Q. 2015. In Press. Chinese medicine amygdalin and β-glucosidase combined with antibody enzymatic prodrug system as a feasible antitumor therapy. Chin J Integr Med. doi: 10.1007/s11655-015-2154-x, 4 pages

808. Li, Y., Wang, F., Xu, J., Ye, F., Shen, Y., Zhou, J., Lu, W., Wan, X., Ma, D. and Xie, X. 2011. Progressive miRNA expression profiles in cervical carcinogenesis and identification of HPV-related target genes for miR-29. The Journal of Pathology. 224(4): 484-495

809. Li, Y., Zhang, J., Ma, D., Zhang, L., Si, M., Yin, H. and Li, J. 2012. Curcumin inhibits proliferation and invasion of Notch-1 signaling. FEBS Journal. 279(12): 2247-2259

810. Li, Y., Zhang, T., Korkaya, H., Liu, S., Lee, H., Newman, B., Yu, Y., Clouthier, G. S., Schwartz, S. J., Wicha, M. S. and Sun, D. 2010. Sulforaphane, a dietary component of broccoli/broccoli sprouts, inhibits breast cancer stem cells. Clin Cancer Res. 16(9): 2580-2590

811. Li, Y., Zhang, X., Zhang, J., Li, Y., Liu, W., Wang, Z., Wang, Y. and Si, S. 2014. A small molecule, MTBT, prevents cancer cell growth by activating p38 MAPK. Anticancer Drugs. 25(4): 423-32

812. Li, Z., Zhang, L., Zhao, Y., Li, H., Xiao, H., Fu, R., Zhao, C., Wu, H. and Li, Z. 2013. Cell-surface GRP78 facilitates colorectal cancer cell migration and invasion. The International Journal of Biochemistry and Cell Biology. 45(5): 987-994

813. Liang, W., Li, X., Li, C., Liao, L., Gao, B., Gan, H., Yang, Z., Liao, L. and Chen, X. 2011. Quercetin-mediated apoptosis via activation of the mitochondrial-dependent pathway in MG-63 osteosarcoma cells. Molecular Medicine Reports. 4(5): 1017-23

814. Liang, Y., Brekken, R. A. and Hyder, S. M. 2006. Vascular endothelial growth factor induces proliferation of breast cancer cells and inhibits the anti-proliferative activity of anti-hormones. Endocr Relat Cancer. 13(3): 905-19

815. Liang, Y., Qi, W., Guo, W., Wang, C., Hu, Z. and Li, A. 2018. Genistein and daidzein induce apoptosis of colon cancer cells by inhibiting the accumulation of lipid droplets. Food and Nutrition Research. 62: 1384, https://dx.doi.org/10.29219/fnr.v62.1384

816. Lİggins, J., Bluck, L. J., Runswick, S., Atkinson, C., Coward, W. A. and Bingham, S. A. 2000. Daidzein and genistein content of fruits and nuts. J nutr Biochem. 11(6): 326-31

817. Lightfoot, H. L., Miska, A. E. and Balasubramanian, S. 2016. Identification of small molecule inhibitorsd of the Lin28-mediated blockage of pre-let-7g processing. Org Biomol Chem. 14(43): 10208-10216

818. Lilja, A., Nordborg, C., Brun, A., Salford, L. G. and Aman, P. 2001. Expression of the IL-6 family cytokines in human brain tumors. Int J Oncol. 19(3): 495-9

819. Lim, J. Y., Kim, D., Kim, B. R., Jun, J. S., Yeom, J. S., Park, J. S., Seo, J., Park, C. H., Woo, H. O., Youn, H., Baik, S., Lee, W., Cho, M. and Rhee, K. 2016. Vitamin C induces apoptosis in AGS cells via production of ROS of mitochondria. Oncol Lett. 12(5): 4270-4276

820. Lim, J., Lee, S. H., Cho, S., Lee, I. S., Kang, B. Y. and Choi, H. J. 2013. 4-methoxychalcone enhances cisplatin-induced oxidative stress and cytotoxicity by inhibiting the Nrf2/ARE-mediated defense mechanism in A549 lung cancer cells. Mol Cells. 36(4): 340-6

821. Lim, Y. J., Lee, Y. J., Byun, J. B. and Kim, H. S. 2015. Fisetin targets phosphatidylinositol-3-kinase and induces apoptosis of human B lymphoma Raji cells. Toxicology Reports. 2: 984-989, doi: 10.1016/j.toxrep.2015.07.004

822. Limagne, E., Lancon, A., Delmas, D., Cherkaoui-Malki, M. and Latruffe, N. 2016. Resveratrol interferes with IL-1B-induced pro-inflammatory Paracrine interaction between primary

chondrocytes and macrophages. Nutrients. 8:5, doi: 10.3390/nu8050280, 11 pages

823. Limantara, L., Dettling, M., Indrawati, R., Indriatmoko and Brotosudarmo, T. H. P. 2015. Analysis on the chlorophyll content of commercial green leafy vegetables. Procedia Chemistry. 14: 225-231, doi: 10.1016/j.proche. 2015. 03.032

824. Limtrakul, P., Khantamat, O. and Pintha, K. 2005. Inhibition of P-glycoprotein function and expression by kaempferol and quercetin. J Chemother. 17(1): 86-95, doi: 10.1179/joc.2005.17.1.86

825. Lin, C. H., Cheng, H. W., Ma, H. P., Wu, C. H., Hong, C. Y. and Chen, B. C. 2011. Thrombin induces NF-kappaB activation and IL-8/CXCL8 expression in lung epithelial cells by a Rac1-dependent PI3K/Akt pathway. J Biol Chem. 286(12):10483-94

826. Lin, C., Chao, A., Wang, T. H., Hsueh, S., Lee, Y. S., Wu, T. I., Chao, A. S., Hwang, H. J., Chou, H. H., Chang, T. C. and Lai, C. H. 2014. A dual tyrosine kinase inhibitor lapatinib suppresses overexpression of matrix metallopeptidase 1 (MMP1) in endometrial cancer. J Mol Med (Berl). 92(9): 969-81

827. Lin, C., Chen, H., Lin, C., Wu, H., Sheu, J. J. and Chen, H. 2017. Apigenin-induced lysosomal degradation of β-catenin in Wnt/β-catenin signaling. SciRep. 7:372, doi: 10.1038/s41598-017-00409-z, 17 pages

828. Lin, C., McGough, R., Aswad, B., Block, J. A. and Terek, R. 2004. Hypoxia induces HIF-1alpha and VEGF expression in chondrosarcoma cells and chondrocytes. J Orthop Res. 22(6):1175-81

829. Lin, C., Shen, S., Hou, W., Yang, L. and Chen, Y. 2008. Heme oxygenase-1 inhibits breast cancer invasion via suppressing the expression of matrix metalloproteinase-9. Molecular Cancer Therapeutics. 7(5): 1195-206

830. Lin, C., Wang, L., Wang, H., Yang, L., Guo, H. and Wang, X. 2013. Tanshinone IIA inhibits breast cancer stem cells growth in vitro and in vivo through attenuation of IL-6/STAT-3/NF-kB signaling pathways. Journal of Cellular Biochemistry. 114(9): 2061-70

831. Lin, H. Y., Huang, B. R., Yeh, W. L., Lee, C. H., Huang, S. S., Lai, C. H., Lin, H. and Lu, D. Y. 2014. Antineuroinflammatory effects of lycopene via activation of adenosine monophosphate-activated protein kinase-α1/heme oxygenase-1 pathways. Neurobiol Aging. 35(1):191-202, doi: 10.1016/j.neurobiolaging.2013.06.020
832. Lin, H., Chiang, M., Chang, P. and Chau, L. 2015. Myeloid heme oxygenase-1 promotes metastatic tumor colonization in mice. Cancer Science. 106(3): 299-306
833. Lin, H., Xiong, W., Zhang, X., Liu, B., Zhang, W., Zhang, Y., Cheng, J. and Huang, H. 2011. Notch-1 activation-dependent p53 restoration contributes to resveratrol-induced apoptolsis in glioblastoma cells. Oncol Rep. 26(4): 925-30
834. Lin, H., Yeh, W., Lee, C., Huang, S., Lai, C., Lin, H. and Lu, D. 2014. Antineuroinflammatory effects of lycopene via activation of adenosine monophosphate-activated protein kinase-α1/heme oxygenase-1 pathways. Neurobiology of Aging. 35:191-202, http: // dx.doi.org / 10.1016 / j. neurobiolaging . 2013 . 06 . 020
835. Lin, J., Zhang, S. M., Wu, K., Willet, W. C., Fuchs, C. S. and Giovannucci, E. 2006. Flavonoid intake and colorectal cancer risk in men and women. Am J Epidemiol. 164(7): 644-651
836. Lin, S. and Gregory, R. 2015. Identification of small molecule inhibitors of Zcchc11 TUTase activity. RNA Biol. 12(8): 792-800
837. Lin, W., Wu, R. T., Wu, T:, Khor, T. O., Wang, H. and Kong, A. N. 2008. Sulforaphane suppressed LPS-induced inflammation in mouse peritoneal macrophages through Nrf2 dependent pathway. Biochem Pharmacol. 76(8): 967-73
838. Lin, X., Shen, J., Peng, D., He, X., Xu, C., Chen, X., Tanyi, J. L., Montone, K., Fan, Y., Huang, Q., Zhang, L. and Zhong, X. 2018. RNA-binding protein LIN28B inhibits apoptosis through regulation of the Akt2/Foxo3A/BIM axis in ovarian cancer cells. Signal Transduct Target Ther. 3: 23, doi: 10.1038/ s41392-018-0026-5
839. Lin, Y., Krogh-Andersen, K., Hammarström, L. and Marcotte, H. 2017. *Lactobacillus* delivery of bioactive interleukin-22. Microbial Cell Factories. 16:148, doi: 10.1186/s12934-017-0762-1, 8 pages

840. Linardi, L. R. and Natalini, C. C. 2006. Multi-drug resistance (MDR1) gene and P-glycoprotein influence on pharmacokinetic and pharmacodynamic of therapeutic drugs. Cienc. Rural. 36(1): 336-341, http://dx.doi.org/10.1590/S0103-84782006000100056

841. Lind, S. D. 2004. Arginine and Cancer. J Nutr. 134(10): 2837S-2841S

842. Lindsay, J., Jiao, X., Sakamaki, T., Casimiro, C. M., Shirley, A. L., Tran, H. T., Ju, X., Liu, M., Li, Z., Wang, C., Katiyar, S., Rao, M., Allen, G. K., Glazer, I. R., Ge, C., Stanley, P., Lisanti, P. M., Rui, H. and Pestell, G. R. 2008. ErbB2 induces Notch activity and function in breast cancer cells. Clin Transl Sci. 1(2): 107-115

843. Ling, R., Zhou, Y., Zhou, L., Dai, D., Wu, D., Mi, L., Mao, C. and Chen, D. 2018. Lin28/microRNA-let-7a promotes metastasis under circumstances of hyperactive Wnt signaling in esophageal squamous cell carcinoma. Molecular Medicine Reports. 17(4): 5265-5271

844. Liu, B., Qu, L. and Yan, S. 2015. Cyclooxygenase-2 promotes tumor growth and suppresses tumor immunity. Cancer Cell Int. 15: 106, doi: 10.1186/s12935-015-0260-7

845. Liu, G., Bibus, D.M., Bode, A.M., Ma, W., Holman, R.T. and Dong, Z. 2001. Omega 3 but not omega 6 fatty acids inhibit AP-1 activity and cell transformation in JB6 cells. Proceedings of the National Academy of Sciences. 98(13): 7510–7515.

846. Liu, H., Huang, G., Zhang, X., Ren, D. and Wilson, J. X. 2010. Folic acid supplementation stimulates Notch signaling and cell proliferation in embryonic neural stem cells. J Clin Biochem Nutr. 47(2): 174-180

847. Liu, J., Li, X., Yue, Y., Li, J., He, T. and He, Y. 2005. The inhibitory effect of quercetin on IL-6 production by LPS-stimulated neutrophiles. Cellular & Molecular Immunology. 2(6): 455-460

848. Liu, L. Z., Fang, J., Zhou, Q., Hu, X., Shi, X. and Jiang, B. H. 2005. Apigenin inhibits expression of vascular endothelial growth factor and angiogenesis in human lung cancer cells: implication of chemoprevention of lung cancer: Mol Pharmacol. 68(3): 635-43

849. Liu, L., Hou, L., Gu, S., Zuo, X., Meng, D., Luo, M., Zhang, X., Huang, S. and Zhao, X. 2015. Molecular mechanism of epigallocatechin-3-gallate in human esophageal squamous cell carcinoma in vitro and in vivo. Oncology Reports. 33:297-303, doi: 10.3892/or.2014.3555μμ

850. Liu, M., Liao, K., Yu, C., Li, X., Liu, S. and Yang, S. 2014. Puerarin alleviates neuropathic pain by inhibiting neuroinflammation in spinal cord. Mediators Inflamm. 2014:485927, 9 pages, doi: 10.1155/2014/485927

851. Liu, M., Yasmeen, R., Fukagawa, N. K., Yu, L., Kim, Y. S. and Wang, T. T. Y. 2017. Dose-dependent responses of I3C and DIM on T-cell activation in the human T lymphocyte Jurkat cell line. Int J Mol Sci. 18(7): 1409, doi: 10.3390/ijms18071409

852. Liu, N., Rowley, B. R., Bull, C. O., Schneider, C., Haegebarth, A., Schatz, C. A., Fracasso, P. R., Wilkie, D. P., Hentemann, M., Wilhelm, S. M., Scott, W. J., Numberg, D. and Ziegelbauer, K. 2013. BAY 80-6946 is a highly selective intravenous PI3K inhibitor with potent p110α and p110δ activities in tumor cell lines and xenograft models. Mol Cancer Ther. 12(11): 2319-30

853. Liu, P. L., Tsai, J. R., Charles, A. L., Hwang, J. J., Chou, S. H., Ping, Y. H., Lin, F. Y., Chen, Y. L., Hung, C. Y., Chen, W. C., Chen, Y. H. and Chong, W. 2010. Resveratrol inhibits human lung adenocarcinoma cell metastasis by suppressing heme oxygenase 1-mediated nuclear factor-kappaB pathway and subsequently downregulating expression of matrix metalloproteinases. Mol Nutr Food Res. 54(52): S196-204, doi: 10.1002/mnfr.200900550

854. Liu, T., Wu, X., Wang, Y., Zhong, T., Wu, T., Liu, F., Wang, W., Jiang, G. and Xie, M. 2016. Folate-targeted star-shaped cationic copolymer co-delivering docetaxel and MMP-9 siRNA for nasopharyngeal carcinoma therapy. Oncotarget. 7(27): 42017-42030

855. Liu, W., Chang, J., Chong, I., Hung, Y., Chen, Y., Huang, W., Kuo, H., Hsieh, C. and Liu, P. 2017. Curcumin inhibits Lin-28A through the activation of miRNA-98 in the lung cancer cell line A549. Molecules. 22: 929, doi: 10.3390/molecules22060929, 24 pages

856. Liu, W., Kou, B., Ma, Z., Tang, X., Lv, C., Ye, M., Chen, J., Li, L., Wang, X. and He, D. 2015. Tetrandrine suppresses proliferation, induces apoptosis, and inhibits migration and invasion in human prostate cancer cells. Asian J Androl. 17(5): 850-853

857. Liu, W., Litwack, E. D., Stanley, J. M., Langford, K. J., Lander, D. A. and Sanderson, D. R. 1998. Heparan sulfate proteoglycans as adhesive and anti-invasive molecules. Syndecans and glypican have distinct functions. The Journal of Biological Chemistry. 273(35): 22825-22832

858. Liu, X., Li, L., Lv, L., Chen, D., Shen, L. and Xie, Z. 2015. Apigenin inhibits the proliferation and invasion of osteosarcoma cells by suppressing the Wnt/B-catenin signaling pathway. Oncol Rep. 34(2): 1035-41

859. Liu, X., Xue, X., Wang, H. and Xu, X. 2016. Genistein modulates MMP-26 and estrogen receptor expression in endometrial cancer cells. Journal of Traditional Chinese Medical Sciences. 3(4): 242-247

860. Liu, Z. J., Shirakawa, T., Li, Y., Soma, A., Oka, M., Dotto, G. P., Fairman, R. M., Velazquez, O. C. and Herlyn, M. 2003. Regulation of Notch 1 and DII4 by vascular endothelial growth factor in arterial endothelial cells: implications for modulating arteriogenesis and angiogenesis. Mol Cell Biol. 23(1): 14-25, doi: 10.1128/mcb.23.1.14-25.2003

861. Liu, Z., Yang, Z., Zhou, J., Zhang, H., Huang, Q., Dang, L., Liu, G. and Tao, K. 2014. Curcumin regulates hepatoma cell proliferation and apoptosis through the Notch signaling pathway. Int J Clin Exp Med. 7(3): 714-718

862. Lodola, A., Giorgio, C., Incerti, M., Zanotti, I. and Tognolini, M. 2017. Targeting Eph/ephrin system in cancer therapy. Eur J Med Chem. 142:152-162, doi: 10.1016/j.ejmech.2017.07.029

863. Loignon, M., Miao, W., Hu, L., Bier, A., Bismar, T. A., Scrivens, P. J., Mann, K., Basik, M., Bouchard, A., Fiset, P. O., Batist, Z. and Batist, G. 2009. Cul3 overexpression depletes Nrf2 in breast cancer and is associated with sensitivity to carcinogens, to oxidative stress, and to chemotherapy. Mol Cancer Ther. 8(8): 2432-40

864. Lomonosova, E. and Chinnadurai, G. 2008. BH3-only proteins in apoptosis and beyond: an overviewer. Oncogene. 27(Suppl 1): S2-19, doi: 10.1038/onc.2009.39

865. Lonetti, A., Antunes, L. I., Chiarini, F., Orsini, E., Buontempo, F., Ricci, F., Tazzari, L. P., Pagliaro, P., Melchionda, F., Pession, A., Bertaina, A., Locatelli, F., McCubrey, A. J., Barata, T. J. and Martelli, M.A. 2014. Activity of the pan-class I phosphoinositide 3-kinase inhibitor NVP-BKM120 in T-cell acute lymphoblastic leukemia. Leukemia. 28(6): 1196-206

866. Long, H., Yang, H., Lin, Y., Situ, D. and Liu, W. 2013. Fish oil-supplemented parenteral nutrition in patients following esophageal cancer surgery: effect on inflammation and immune function. Nutr Cancer. 65(1):71-5.

867. Long, Q., Peng, Y., Tang, Z. and Wu, C. 2014. Role of endometrial cancer abnormal MMR protein in screening Lynch-syndrome families. Int J Clin Exp Pathol. 7(10): 7297-7303

868. Lopes-Rodrigues, V., Oliveira, A., Correia-da-Silva, M., Pinto, M., Lima, R. T., Sousa, E. and Vasconcelos, M. H. 2017. A novel curcumin derivative which inhibits P-glycoprotein, arrests cell cycle and induces apoptosis in multidrug resistance cells. Bioorganic & Medicinal Chemistry. 25: 581-596, http://dx.doi.org/10.1016/j.bmc.2016.11.023

869. Lopez-Guerra, M., Xargay-Torrent, S., Rosich, L., Montraveta, A., Roldan, J., Matas-Cespedes, A., Vilamor, N., Aymerich, M., Lopez-Otin, C., Perez-Galan, P., Roue, G., Campo, E. and Colomer, D. 2015. The γ-secretase inhibitor PF-03084014 combined with fludarabine antagonizes migration, invasion and angiogenesis in NOTCH1-mutated CLL cells. Leukemia. 29: 96-106, doi: 10.1038/leu.2014.143

870. Lopez-Lazaro, M. 2009. Distribution and biological activities of the flavonoid luteolin. Mini Rev Med Chem. 9(1): 31-59, doi: 10.2174/138955709787001712

871. Lorenz, H. M. 2003. T-cell-activation inhibitors in rheumatoid arthritis. BioDrugs. 17(4): 263-70

872. Lorenz, M., Urban, J., Engelhardt, U., Baumann, G., Stangl, K. and Stangl, V. 2009. Green and black tea are equally potent

stimuli of NO production and vasodilation: New insights into tea ingredients involved. Basic Research in Cardiology. 104(1): 100-110, doi: s00395-008-0759-3

873. Losonczy, K. G., Harris, T. B. and Havlik, R. J. 1996. Vitamin E and vitamin C supplement use and risk of all-cause and coronary heart disease mortality in older persons: the established populations for epidemiologic studies of the elderly. Am J Clin Nutr. 64(2): 190-6

874. Lowe, J., Araujo, J., Yang, J., Reich, M., Oldendorp, A., Shiu, V., Quarmby, V., Lowman, H., Lien, S., Gaudreault, J. and Maia, M. 2007. Ranibizumab inhibits multiple forms of biologically active vascular endothelial growth factor in vitro and in vivo. Exp Eye Res. 85(4): 425-30

875. Lu, H. F., Tung, W. L., Yang, J. S., Huang, F. M., Lee, C. S., Huang, Y. P., Liao, W. Y., Chen, Y. L. and Chung, J. G. 2012. In vitro suppression of growth of murine WEHI-3 leukemia cells and in vivo promotion of phagosytosis in a leukemia mice model by indole-3-carbinol. J Agric Food Chem. 60(31): 7634-43

876. Lu, H., Chie, Y., Yang, M., Lee, C., Fu, J., Yang, J., Tan, T., Wu, S., Ma, Y., Ip, S. and Chung, J. 2010. Apigenin induces caspase-dependent apoptosis in human lung cancer A549 cells through Bax-and Bcl-2-triggered mitochondrial pathway. International Journal of Oncology. 36:1477-1484, doi:10.3892/ijo_00000634

877. Lu, H., Ouyang, W. and Huang, C. 2006. Inflammation, a key event in cancer development. Mol Cancer Res. 4(4): 221-33

878. Lu, J., Li, Z., Guo, L. and Zhang, L. 2018. Sesquiterpene lactones with COX-2 inhibition activity from *Artemisia lavandulaefolia*. Chemistry & Biodiversity. 15: e1700548, doi: 10.0002/cbdv.201700548, 7 pages

879. Lu, J., Wang, Z., Li, S., Xin, Q., Yuan, M., Li, H., Song, X., Gao, H., Pervaiz, N., Sun, X., Lv, W., Jing, T. and Zhu, Y. 2018. Quercetin inhibits the migration and invasion of HCCLM3 cells by suppressing the expression of p-Akt1, matrix metalloproteinase (MMP) MMP-2, and MMP-9. Med Sci Monit. 24: 2583-2589, doi: 10.12659/MSM.906172

880. Lü, J.L., Li, Z., Guo, L.M. and Zhang, L.B. 2018. Sesquiterpene lactones with COX-2 inhibition activity from *Artemisia lavandulaefolia*. Chem Biodivers. 15(5):e1700548, doi: 10.1002/cbdv.201700548

881. Lu, M., Ji, J., Jiang, Y., Chen, Z., Yuan, Z., You, Q. and Jiang, Z. 2016. An inhibitor of the Keap1-Nrf2 protein-protein interaction protects NCM460 colonic cells and alleviates experimental colitis. Scientific Reports. 6: 26585, doi: 10.1038/srep26585, 13 pages

882. Lu, N., Du, Y., Li, H., Luo, Y., Ouyang, B., Chen, Y., Yang, Y. and Yang, L. 2018. Omega-6 fatty acids down-regulate matrix metalloproteinase expression in a coronary heart disease-induced rat model. International Journal of Experimental Pathology. Doi: 10.1111/iep.12293, 8 pages

883. Lu, Q., Hung, J., Heber, D., Go, V.L.W., Reuter, V. E., Cordon-Cardo, C., Scher, H. I., Marshall, J. R. and Zhang, Z. 2001. Inverse associations between plasma lycopene and other carotenoids and prostate cancer. Cancer Epidemiology, Biomarkers and Prevention. 10(7): 749-56

884. Lu, Y. L., Ou, N. and Lu, Q. 2013. Antioxidant induces DNA damage, cell death and mutagenicity in human lung and skin normal cells. Scientific Reports. 3: 3169, doi: 10.1038/srep03169, 11 pages

885. Lu, Y., Wang, Y., Zhang, M., Liu, L., Li, F., Zhang, J., Ye, M., Zhao, H., Zhao, J., Yan, B., Yang, A., Zhang, R., Li, X. and Ren, X. 2016. HER2-siRNA delivered by EGFR-specific single chain antibody inhibits NSCLC cell proliferation and tumor growth. Oncotarget. 7(17): 23594-23607

886. Luo, H., Daddysman, M. K., Rankin, G. O., Jiang, B. and Chen, Y. C. 2010. Kaempferol enhances cisplatin's effect on ovarian cancer cells through promoting apoptosis caused by down regulation of cMyc. Cancer Cell International. 10:16, doi: 10.1186/1475-2867-10-16, 9 pages

887. Luo, H., Jiang, B. H., King, S. M. and Chen, Y. C. 2008. Inhibition of cell growth and VEGF expression in ovarian cancer cells by flavonoids. Nutr Cancer. 60(6): 800-9

888. Luo, H., Rankin, G. O., Juliano, N., Jiang, B. and Chen, Y. C. 2012. Kaempferol inhibits VEGF expression in vitro angiogenesis through a novel ERK-NF-kB-cMyc-p21 pathway. Food Chem. 130(2): 321-328

889. Luo, S., Wang, Z., Kansara V., Pal, D. and Mitra, A. K. 2008. Activity of a sodium-dependent vitamin C transporter (SVCT) in MDCK-MDR1 cells and mechanism of ascorbate uptake. Int J Pharm. 358(1-2): 168-176, doi: 10.1016/j.ijpharm.2008.03.002

890. Lustig, R. H. 2013. It's 'Alcohol without the buzz'[1,2,3]. Adv Nutr. 4(2): 226-235

891. Lv, J., Xiong, W., Lei, T., Wang, H., Sun, M., Hao, E., Wang, Z., Huang, X., Deng, S., Deng, J. and Wang, Y. 2017. Amygdalin ameliorates the progression of atherosclerosis in LDL receptor-deficient mice. Mol Med Rep. 16(6): 8171-8179

892. Lyons, M. M., Yu, C., Toma, R. B., Cho, S. Y., Reiboldt, W., Lee, J. and van Breeman, R. B. 2003. Resveratrol in raw and baked blueberries and bilberries. J Agric Food Chem. 51(20): 5867-5870

893. Ma, D., Fang, Q., Wang, P., Gao, R., Wu, W., Lu, T., CaO, L., Hu, X. and Wang, J. 2015. Induction of heme oxygenase-1 by Na+-H+ exchanger 1 protein plays a crucial role in imatinib-resistant chronic myeloid leukemia cells. The Journal of Biological Chemistry. 290(20): 12558-71

894. Ma, J. W., Zhang, Y., Li, R., Ye, J. C., Li, H. Y., Zhang, Y. K., Ma, Z. L., Li, J. Y., Zhong, X. Y. and Yang, X. 2015. Tetrandrine suppresses human glioma growth by inhibiting cell survival, proliferation and tumour angiogenesis through attenuating STAT3 phosphorylation. Eur J Pharmacol. 764: 228-239, doi: 10.1016/j.ejphar.2015.06.017

895. Ma, X., Bai, J., Xie, G., Liu, Y., Shuai, X. and Tao, K. 2017. Prognostic significance of microRNA-101 in solid tumor: A meta-analysis. Plos One. 12(7): e0180173. https: // doi. org/10.1371/journal.pone.0180173, 16 pages

896. MacLean, C.H., Newberry, S.J., Mojica, W.A. et al. (2006). Effects of omega-3 fatty acids on cancer risk. The Journal of American Medical Association. 295(4): 403–415.

897. MacNee, W., Allan, R. J., Jones, I., De Salvo, M. C. and Tan, L. F. 2013. Efficacy and safety of the oral p38 inhibitor PH-797804 in chronic obstructive pulmonary disease: a randomized clinical trial. Thorax. 68(8): 738-45

898. Madarampalli, B. and Ahmed, S. 2017. Epigallocatechin-3-gallate (EGCG) inhibits IL-6 induced CRP synthesis and ameliorates adiponectin expression in Hep3B cells. The FASEB Journal. 31:1_supplement, 964.18-964.18

899. Mahmoed, M. Y. and Rezq, A. A. 2013. Hepatoprotective effect of avocado fruits against carbon tetrachloride-induced liver damage in male rats. World Applied Sciences Journal. 21(10):1445-1452

900. Mai, T., Wang, W., Crespo, J., Zhang, H., Wang, W., Wei, S., Zhao, L., Vatan, L., Shao, I., Szeliga, W., Lyssiotis, C., Liu, J. R., Kryczek, I. and Zou, W. 2017. Oxidative stress controls regulatory T cell apoptosis and suppressor activity and PD-L1-blockade resistance in tumor. Nat Immunol. 18(12): 1332-1341

901. Mai, Z., Blackburn, G. L. and Zhou, J. 2007. Genistein sensitizes inhibitory effect of tamoxifen on the growth of estrogen receptor-positive and HER2-overexpressing human breast cancer cells. Carcinog. 46(7): 534-542

902. Maira, S. M., Stauffer, F., Brueggen, J., Furet, P., Schnell, C., Fritsch, C., Brachmann, S., Chene, P., De Pover, A., Schoemaker, K., Fabbro, D., Gabriel, D., Simonen, M., Murphy, L., Finan, P., Sellers, W. and Garnia-Echeverria, C. 2008. Identification and characterization of NVP-BEZ235, a new orally available dual phosphatidylinositol 3-kinase/mammalian target of rapamycin inhibitor with potent in vivo antitumor activity. Mol Cancer Ther. 7(7): 1851-63

903. Maj, E., Filip-Psurska, B., Milczarek, M., Psurski, M., Kutner, A. and Wietrzyk, J. 2018. Vitamin D derivatives potentiate the anticancer and anti-angiogenic activity of tyrosine kinase inhibitors in combination with cytostatic drugs in an A549 non-small cell lung cancer model. International Journal of Oncology. 52:337-366, doi: 10.3892/ijo.2017.4228

904. Majumder, M., Xin, X., Liu, L., Tutunea-Fatan, E., Rodriguez-Torres, M., Vincent, K., Postovit, L. M., Hess, D. and Lala, P K. 2016. COX-2 induces breast cancer stem cells via EP4/PI3K/Akt/Notch/Wnt axis. Stem Cells. 34(9): 2290-305

905. Makarevic, J., Rutz, J., Juengel, E., Kaulfuss, S., Reiter, M., Tsaur, I., Bartsch, G., Haferkamp, A. and Blaheta, A. R. 2014. Amygdalin blocks bladder cancer cell growth in vitro by diminishing cyclin A and cdk2. 9(8): e105590, doi: 10.1371/journal.pone.0105590, 9 pages

906. Malik, F., Korkaya, H., Clouthier, S. G. and Wicha, M. S. 2012. Lin28 and HER2: two stem cell regulators conspire to drive aggressive breast cancer. Cell Cycle. 11(15): 2780-1

907. Malila, N., Taylor, R. P., Virtanen, J. M., Korhonen, P., Huttunen, K. J., Albanes, D. and Virtamo, J. 2002. Effects of alpha-tocopherol and beta-carotene supplementation on gastric cancer incidence in male smokers (ATBC Study Finland). Cancer Causes and Control. 13(7): 617-623

908. Malkomes, P., Lunger, I., Luetticke, A., Oppermann, E., Haetscher, N., Serve, H., Holzer, K., Bechstein, W. O. and Rieger, M. A. 2016. Selective AKT inhibition by MK-2206 represses colorectal cancer-initiating stem cells. Ann Surg Oncol. 23(9): 2949-57

909. Malloy, K. M., Wang, J., Clark, L. H., Fang, Z., Sun, W., Yin, Y., Kong, W., Zhou, C. and Bae-Jump, V. 2018. Novasoy and genistein inhibit endometrial cancer cell proliferation through disruption of the Akt/mTOR and MAPK pathway. Am J Transl Res. 10(3): 784-795

910. Manach, C., Scalbert, A., Morand, C., Remesy, C. and Jimenez, L. 2004. Polyphenols: food sources and bioavailability. Am J Clin Nutr. 79(5): 727-47

911. Maniati, E., Bossard, M., Cook, N., Candido, B. J., Emami-Shahri, N., Nedospasov, S. A., Balkwill, R. F., Tuveson, D. A. and Hagemann, T. 2011. Crosstalk between the canonical NF-kB and Notch signaling pathways inhibits PparΥ expression and promotes pancreatic cancer progression in mice. J Clin Invest. 121(12): 4685-4699

912. Mannick, B. J., Schonhoff, C., Papeta, N., Ghafourifar, P., Szibor, M., Fang, K. and Gaston, B. 2001. S-Nitrosylation of mitochondrial caspases. J Cell Biol. 154(6): 1111-1116
913. Mansilla, S. F., Bertolin, A. P., Bergoglio, V., Pillaire, M. J., Gonzalez Besteiro, M. A., Luzzani, C., Miriuka, S. G., Cazaux, C., Hoffmann, J. S. and Gottifredi, V. 2016. Cyclin kinase-independent role of p21CDKN1A in the promotion of nascent DNA elongation in unstressed cells. Elife. 5:e18020, doi: 10.7554/eLife.18020, 26 pages
914. Mao, C., Tao, Z., Chen, Z., Chen, C., Chen, S. and Wan, L. 2014. Indole-3-carbinol inhibits nasopharyngeal carcinoma cell growth in vivo and in vitro through inhibition of the PI3K/Akt pathway. Exp Ther Med. 8(1): 207-212, doi:10.3892/etm.2014.1696
915. Marini, J. C. 2017. Interrelationships between glutamine and citrulline metabolism. Curr Opin Clin Nutr Metab Care. 19(1): 62-66, doi: 10.1097/MCO.0000000000000233
916. Marinissen, M. J., Tanos, T., Bolos, M., de Sagarra, M. R., Coso, O. A. and Cuadrado, A. 2006. Inhibition of heme oxygenase-1 interferes with the transforming activity of the Kaposi sarcoma herpesvirus-encoded G protein-coupled receptor. The Journal of Biological Chemistry. 281(16): 11332-11346
917. Markman, B., Atzori, F., Perez-Garcia, J., Tabernero, J. and Baselga, I. 2010. Status of PI3K inhibition and biomarker development in cancer therapeutics. Ann Oncol. 21(4): 683-691
918. Marsili, V., Calzuola, I. and Gianfranceschi, G. L. 2004. Nutritionl relevance of wheat sprouts containing high levels of organic phosphates and antioxidant compounds. J Clin Gastroenterol. 38(6 Suppl): S123-6
919. Martin, J. C., Wolk, K., Beriou, G., Abidi, A., Witte-Händel, E., Louvet, C., Kokolakis, G., Drujont, L., Dumoutier, L., Renauld, J. C., Sabat, R. and Josien, R. 2017. Limited presence of IL-22 binding protein, a natural IL-22 inhibitor, strengthens psoriatic skin inflammation. J Immunol. 198(9): 3671-3678
920. Martini, M., Testi, M. G., Pasetto, M., Picchio, M. C., Innamorati, G., Mazzocco, M., Ugel, S., Cingarlini, S., Bronte, V., Zanovello,

P., Krampera, M., Mosna, F., Cestari, T., Riviera, A. P., Brutti, N., Barbieri, O., Matera, L., Tridente, G., Colombatti, M. and Sartoris, S. 2010. IFN-gamma-mediated upmodulation of MHC class/expression activates tumor-specific immune response in a mouse model of prostate cancer. Vaccine. 28(20): 3548-57

921. Maruti, S. S., Ulrich, C. M. and White, E. 2009. Folate and one-carbon metabolism nutrients from supplements and diet in relation to breast cancer risk. Am J Clin Nutr. 89(2):624-33

922. Maruyama, T., Kono, K., Mizukami, Y., Kawaguchi, Y., Mimura, K., Watanabe, M., Izawa, S. and Fujii, H. 2010. Distribution of Th17 cells and FoxP3 (+) regulatory T cells in tumor filtrating lymphocytes, tumor-draining lymph nodes and peripheral blood lymphocytes in patients with gastric cancer. Cancer Sci. 101(9): 1947-54

923. Masur, K., Vetter, C., Hinz, A., Tomas, N., Henrich, H., Niggemann, B. and Zanker, K. S. 2011. Diabetogenic glucose and insulin concentrations modulate transcriptome and protein levels involved in tumor cell migration, adhesion and proliferation. Br J Cancer. 104(2): 345-352

924. Matsunaga, S., Asano, T., Tsutsuda-Asano, A. and Fukunaga, Y. 2006. Indomethacin overcomes doxorubicin resistance with inhibiting multi-drug resistance protein 1 (MRP1). Cancer Chemother Pharmacol. 58(3): 348-53

925. Matsuo, Y., Sawai, H., Ochi, N., Yasuda, A., Sakamoto, M., Takahashi, H., Funahashi, H., Takeyama, H. and Guha, S. 2010. Proteasome inhibitor MG132 inhibits angiogenesis in pancreatic cancer by blocking NF-kappaB activity. Dig Dis Sci. 55(4): 1167-76

926. Mayerhofer, M., Florian, S., Krauth, M. T., Aichberger, K. J., Bilban, M., Marculescu, R., Printz, D., Fritsch, G., Wagner, O., Selzer, E., Sperr, W. R., Valent, P. and Sillaber, C. 2004. Identification of heme oxygenase-1 as a novel BCR/ABL-dependent survival factor in chronic myeloid leukemia. Cancer Res. 64(9): 3148-54

927. Mayne, T. S., Cartmel, B., Lin, H., Zheng, T. and Goodwin, J. W. 2004. Low plasma lycopene concentration is associated with

increased mortality in a cohort of patients with prior, pharynx or laryx cancers. Journal of the American College of Nutrition. 23(1): 34-42 https://doi.org/1.1080/07315724.2004.10719340

928. Mazza, G. and Cottrell, T. 2008. Carotenoids and cyanogenic glycosides in Saskatoon berries (*Amelanchier alnifolia Mutt*). Journal of Food Composition and Analysis. 21(3): 249-254

929. McCall, B., McPartland, C. K., Moore, R., Frank-Kamenetskii, A. and Booth, B. W. 2018. Effects of astaxanthin on the proliferation and migration of breast cancer cells in vitro. Antioxidants. 7: 135, doi: 10.3390/antiox7100135, 8 pages

930. McCarty, M. F. 2012. Metformin may antagonize Lin28 and/or Lin28B activit, thereby boosting let-7 levels and antagonizing cancer progression. Med Hypotheses. 78(2): 262-269

931. McCullough, M. L., Robertson, A. S., Rodriguez, C., Jacobs, E. J., Chao, A., Jonas, C., Calle, E. E., Willett, W. C. and Thun, M. J. 2003. Calcium, vitamin D, dairy products and risk of colorectal cancer in the cancer prevention study II nutrition cohort (United States). Cancer Causes and Control. 14(1):1-12 PMID:12708719

932. McGirt, M. J., Chaichana, K. L., Gathinji, M., Attenello, F., Than, K., Ruiz, A. J., Olivi, A., Quinones-Hinojosa, A. 2008. Persistent outpatient hyperglycemia is independently associated with decreased survival after primary resection of malignant brain astrocytomas. Neurosurgery. 63(2): 286-291

933. McGovern, U. B., Francis, R. E., Peck, B., Guest, S. K., Wang, J., Myatt, S. S., Krol, J., Kwok, J. M., Polchronis, A., Coombes, R. C. and Lam, E. W. 2009. Gefitinib (Iressa) represses FOXM1 expression via FOXO3a in breast cancer. Mol Cancer Ther. 8(3): 582-91

934. Meeran, S. M., Patel, S. N., and Tollefsbol, T. O. 2010. Sulforaphane causes epigenetic repression of hTERT expression in human breast cancer cell lines. Plos One. 5(7): e11457, 13 pages, doi: 10.1371/journal.pone.0011457

935. Meiners, S., Hocher, B., Weller, A., Laule, M., Stangl, V., Guenther, C., Godes, M., Mrozikiewicz, A., Baumann, G. and Stangl, K. 2004. Downregulation of matrix metalloproteinases

and collogens and suppression of cardiac fibrosis by inhibition of the proteasome. Hypertension. 44: 471-477, doi: 10.1161/01. HYP.0000142772.71367.65

936. Meissner, M., Reichenbach, G., Stein, M., Hrgovic, I., Kaufmann, R. and Gille, J. 2009. Down-regulation of vascular endothelial growth factor receptor 2 is a major molecular determinant of proteasome inhibitor-mediated antiangiogenic action in endothelial cells. Cancer Research. 69(5): 1976-84

937. Melnik, S., Dvornikov, D., Müller-Decker, K., Depner, S., Stannek, P., Meister, M., Warth, A., Thomas, M., Muley, T., Risch, A., Plass, C., Klingmüller, U., Niehrs, C. and Glinka, A. 2018. Cancer cell specific inhibition of Wnt/β-catenin signaling by forced intracellular acidification. Cell Discovery. 4: 37, doi: 10.1038/s41421-018-0033-2, 17 pages

938. Menheniott, R. T., O'Connor, L., Chionh, Y. T., Dabritz, J., Scurr, M., Rollo, B. N., Ng, Z. G., Jacobs, S., Catubig, A., Kurklu, B., Mercer, S., Minamoto, T., Ong, E. D., Ferrero, L. R., Fox, G. J., Wang, C. T., Sutton, P., Judd, M. L. and Giraud, S. A. 2016. Loss of gastrokine-2 drives premalignant gastric inflammation and tumor progression. J Clin Invest. 126(4): 1383-1400

939. Merkhofer, E. C., Coqswell, P. and Baldwin, A. S. 2010. Her2 activates NF-kB and induces invasion through the canonical pathway involving IKKalpha. Oncogene. 29(8): 1238-48

940. Migita, K., Miyashita, T., Izumi, Y., Koga, T., Komori, A., Maeda, Y., Jiuchi, Y., Aiba, Y., Yamasaki, S., Kawakami, A., Nakamura, M. and Ishibashi, H. 2011. Inhibitory effects of the JAK inhibitor CP690,550 on human CD4+ T lymphocyte cytokine production. BMC Immunology. 12:51, https://doi. org/10.1186/1471-2172-12-51, 10 pages

941. Miki, H., Uehara, N., Kimura, A., Sasaki, T., Yuri, T., Yoshizawa, K. and Tsubura, A. 2012. Resveratrol induces apoptosis via ROS-triggered autophagy in human colon cancer cells. Int J Oncol. 40(4): 1020-8

942. Mikirova, N. and Scimeca, C. R. 2016. Intravenous high-dose ascorbic acid reduces the expression of inflammatory markers

in peripheral mononuclear cells of subjects with metabolic syndrome. Journal of Translational Science. 2(3): 188-195

943. Mikirova, N., Casciari, J., Rogers, A. and Taylor, P. 2012. Effect of high dose intravenous vitamin C on inflammation in cancer patients. J Transl Med. 10(189): 1-10

944. Milder, I. E. J., Arts, I. C. W., van de Putte, B., Venema, D. P. and Hollman, P. C. H. 2005. Intake of the plant lignans secoisolariciresinol, matairesinol, lariciresinol, and pinoresinol in Dutch men and women. British Journal of Nutrition. 93(03): 393-402

945. Miles, E. A., Zoubouli, P. and Calder, P. C. 2005. Differential anti-inflammatory effects of phenolic compounds from extra virgin olive oil identified in human whole blood cultures. Nutrition. 21(3): 389-94

946. Mills, M. L., Wilson, H. and Thies, F. 2012. Lycopene inhibits lymphocyte proliferation through mechanisms dependent on early cell activation. Mol Nutr Food Res. 56: 1034-1042, doi: 10.1002/mnfr.201200047

947. Mimura, N., Fulciniti, M., Gorgun, G., Tai, Y., Cirstea, D., Santo, L., Hu, Y., Fabre, C., Minami, J., Oghuchi, H., Kızıltepe, T., Ikeda, H., Kawano, Y., French, M., Blumenthal, M., Tam, V., Kertesz, N. L., Nalyankar, U. M., Hokenson, M., Pham, T., Zeng, Q., Patterson, J. B., Richardson, P. G., Munshi, N. C. and Anderson, K. C. 2012. Blockage of XBP1 splicing by inhibition of IRE1α is a promising therapeutic option in multiple myeloma. Blood. 119(24): 5772-5781

948. Minai, L., Yeheskely-Hayon, D. and Yelin, D. 2013. High levels of reactive oxygen species in gold nanoparticle-targeted cancer cells following femtosecond pulse irradiation. Scientific Reports. 3: 2146-2156, doi: 10.1038/srep02146

949. Minami, I., Yamada, K., Otsuji, T. G., Yamamoto, T., Shen, Y., Otsuka, S., Kadota, S., Morone, N., Barve, M., Asai, Y., Tenkova-Heuser, T., Heuser, J. E., Uesugi, M., Aiba, K. and Nakatsuji, N. 2012. A small molecule that promotes cardiac differentiation of human pluripotent stem cells under defined, cytokine-and xeno free conditions. Cell Reports. 2(5): 1448-1460

950. Ming, L., Wang, P., Bank, A., Yu, J. and Zhang, L. 2006. PUMA dissociates Bax and Bcl-xL to induce in colon cancer cells. The Journal of Biological Chemistry. 281:16034-16042, doi:10.1074/jbc.M51387200

951. Miranpuri, G. S., Meethal, S. V., Sampene, E., Chopra, A., Buttar, S., Nacht, C., Moreno, C., Moreno, N., Patel, K., Liu, L., Sing, A., Singh, C. K., Hariharan, N., Iskandar, B. and Resnick, D. K. 2017. Folic acid modulates matrix metalloproteinase-2 expression alleviates neuropathic pain and improves functional recovery in spinal cord-injured rats. Ann Neurosci. 24(2): 74-81

952. Mirmiranpour, H., Khaghani, S., Zandieh, A., Khalilzadeh, O. O., Gerayesh-Nejad, S., Morteza, A. and Esteghamati, A. 2012. Amygdalin inhibits angiogenesis in the cultured endothelial cells of diabetic rats. Indian Journal of Pathology and Microbiology. 55(2): 211-214

953. Mishra, D. K. and Kim, M. P. 2017. SR11302, an AP-1 inhibitor, reduces metastatic lesion formation in Ex vivo 4D lung cancer model. Cancer Microenviron. 10(1-3): 95-103

954. Miyake, M., Fujimoto, K., Anai, S., Ohnishi, S., Nakai, Y., Inoue, T., Matsumura, Y., Tomioka, A., Ikeda, T., Okajima, E., Tanaka, N. and Yoshihiko, H. 2010. Inhibition of heme oxygenase-1 enhances the cytotoxic effect of gemcitabine in urothelial cancer cells. Anticancer Research. 30(6): 2145-2152

955. Miyata, Y., Kanda, S., Mitsunari, K., Asai, A. and Sakai, H. 2014. Heme oxygenase-1 expression is associated with tumor aggressiveness and outcomes in patients with bladder cancer: a correlation with smoking intensity. Translational Research. 164(6): 468-476

956. Miyato, Y. and Ando, K. 2004. Apoptosis of human melanoma cells by a combination of lonidamine and radiation. J Radiat Res. 45(2): 189-194

957. Miyazaki, T., Kirino, Y., Takeno, M., Samukawa, S., Hama, M., Tanaka, M., Yamaji, S., Ueda, A., Tomita, N., Fujita, H. and Ishigatsubo, Y. 2010. Expression of heme oxygenase-1 in human leukemic cells and its regulation by transcriptional repressor Bach 1. Cancer Sci. 101(6): 1409-16

958. Mizuma, M., Rasheed, Z. A., Yabuuchi, S., Omura, N., Campbell, N. R., de Wilde, R. F., De Oliveira, E., Zhang Q., Puig, O., Matsui, W., Hidalgo, M., Maitra, A. and Rajeshkumar, N. V. 2012. The gamma secretase inhibitor MRK-oo3 attenuates pancreatic cancer growth in preclinical models. Mol Cancer Ther. 11(9): 1999-2009

959. Mo, M. L., Li, M. R., Chen, Z., Liu, X. W., Sheng, Q. and Zhou, H. M. 2013. Inhibition of the Wnt palmitoyltransferase porcupine suppresses cell growth and downregulates the Wnt/β-catenin pathway in gastric cancer. Oncol Lett. 5(5): 1719-1723

960. Mo, W., Xu, X., Xu, L., Wang, F., Ke, A., Wang, X. and Guo, C. 2011. Resveratrol inhibits proliferation and induces apoptosis through the hedgehog signaling pathway in pancreatic cancer cell. Pancreatology. 11(6): 601-9

961. Moellering, E. R., Cornejo, M., Davis, N. T., Del Bianco, C., Aster, C. J., Blacklow, C. S., Kung, L. A., Gilliland, G. D., Verdine, L. G. and Bradner, E. J. 2009. Direct inhibition of the NOTCH transcription factor complex. Nature. 462(7270): 182-188

962. Moertei, G. C., Fleming, R. T., Rubin, J., Kvols, K. L., Sarna, G., Koch, R., Currie, E. V., Young, W. C., Jones, E. S. and Davignon, P. J. 1982. A clinical trial of amygdalin (laetrile) in the treatment of human cancer. N Engl J Med. 306 (4): 201-6

963. Mohammadi, S., Seyedhosseini, F. S. Behnampour, N. and Yazdani, Y. 2017. Indole-3-carbinol induces G1 cell cycle arrest and apoptosis through aryl hydrocarbon receptor in THP-1 monocytic cell line. Journal of Receptors and Signal Transduction. 37(5): 506-514

964. Mohanty, V., Shah, A., Allender, E., Siddiqui, R. M., Monick, S., Ichi, S., Mania-Farnell, B., McLone, G. D., Tomita, T. and Mayanil, S. C. 2016. Folate receptor alpha upregulates Oct4, Sox2 and Klf4 and downregulates miR-138 and miR-let-7 in cranial crest cells. Stem Cells. 34(11): 2721-2732

965. Mojsin, M., Vicentic, J. M., Schwirtlich, M., Topalovic, V. and Stevanovic, M. 2014. Quercetin reduces pluripotency, migration and adhesion of human teratocarcinoma cell line NT2/D1 by inhibiting Wnt/B-catenin signaling. Food Funct. 5(10): 2564-73

966. Molnar, J., Gyemant, N., Mucsi, I., Molnar, A., SzaBo, M., Körtvelyesi, T., Varga, A., Molnar, P. and Toth, G. 2004. Modulation of multidrug resistance and apoptolsis of cancer cells by selected carotenoids. In vivo. 18(2): 237-244

967. Montaner, B. and Perez-Tomas, R. 2002. Prodigiosin induces caspase-9 and caspase-8 activation and cytochrome c release in Jurkat T cells. Annals of the New York Academy of Sciences. 973: 246-9, doi: 10.1111/j.1749-6632.2002.tb04642.x

968. Moon, H. M., Jeong, K. J., Lee, J. Y., Seol, W. J., Jackson, J. C. and Park, Y. S. 2013. SIRT1, a class III histone deactylase, regulates TNF-α-induced inflammation in human chondrocytes. Osteoarthritis and Cartilage. 21(3): 470-480

969. Moon, S., Choi, S. and Kim, S. H. 2015. In vitro anti-osteoclastogenic activity of p38 inhibitor doramapimod via inhibiting migration of pre-osteoclasts and NFATc1 activity. Journal of Pharmacological Sciences. 129(3): 135-142

970. Moore-Carrasco, R., Busguets, S., Almendro, V., Palanki, M., Lopez-Soriano, F. J. and Argiles, J. M. 2007. The AP-1/NF-kappaB double inhibitor SP100030 can revert muscle wasting during experimental cancer cachexia. Int J Oncol. 30(5): 1239-45

971. Morand, C., Dubray, C., Milenkovic, D., Lioger, D., Martin, J. F., Scalbert, A. and Mazur, A. 2011. Hesperidin contributes to the vascular protective effects of orange juice: a randomized crossover study in healthy volunteers. Am J Clin Nutr. 93: 73-80, doi: 10.3945/ajcn.110.004945

972. Morques, C., Licks, F., Zattoni, I., Borges, B., de Souza, L. E., Marroni, C. A. and Marroni, N. P. 2013. Antioxidant properties of glutamine and its role in VEGF-Akt pathways in portal hypertension gastropathy. World J Gastroenterol. 19(28): 4464-4474

973. Morre, J. D., Morre, M. D., Sun, H., Cooper, R., Chang, J. and Janle, M. E. 2003. Tea catechin synergies in inhibition of cancer cell proliferation and of a cancer specific cell surface oxidase (ECTO-NOX). Pharmacology & Toxicology. 92(5): 234-241

974. Morrow, D., Cullen, P. J., Liu, W., Guha, S., Sweeney, C., Birney, A. Y., Collins, N., Walls, D., Redmond, M. E. and Cahill, A. P.

2009. Sonic Hedgehog induces Notch target gene expression in vascular smooth muscle cells via VEGF-A. Arterioscler Thromb Vasc Biol. 29(7): 1112-1118

975. Mostafavi-Pour, Z., Ramezani, F., Keshavarzi, F. and Samad, N. 2017 The role of quercetin and vitamin C in Nrf2-dependent oxidative stress production in breast cancer cells Oncol Lett. 2017 Mar; 13(3): 1965–1973

976. Moyad, M.A. 2003. The use of complementary/preventive medicine to prevent prostate cancer recurrence/progression following definitive therapy part I-lifestyle changes. Current Opinion in Urology. 13(2): 137–145

977. Mu, C., Jia, P., Yan, Z., Liu, X., Li, X. and Liu, H. 2007. Quercetin induces cell cycle G1 arrest through elevating Cdk inhibitors p21 and p27 in human hepatoma cell line (HepG2). Methods Find Exp Clin Pharmacol. 29(3): 179-83

978. Murphy, N., Norat, T., Ferrari, P., Jenab, M., Bueno-de-Mesquita, B,., Skeie, G., Dahm, C.C., Overvad, K., Olsen, A., Tjønneland, A., Clavel-Chapelon, F., Boutron-Ruault, M.C., Racine, A., Kaaks, R., Teucher, B., Boeing, H., Bergmann, M.M., Trichopoulou, A., Trichopoulos, D., Lagiou, P., Palli, D., Pala, V., Panico, S., Tumino, R., Vineis, P., Siersema, P., van Duijnhoven, F., Peeters, PH., Hjartaker, A., Engeset, D., González, CA., Sánchez, M.J., Dorronsoro, M., Navarro, C., Ardanaz, E., Quirós, J.R., Sonestedt, E., Ericson, U., Nilsson, L., Palmqvist, R., Khaw, K.T., Wareham, N., Key, T.J., Crowe, FL., Fedirko, V., Wark, P.A., Chuang, S.C. and Riboli E. 2012. Dietary fibre intake and risks of cancers of the colon and rectum in the European prospective investigation into cancer and nutrition (EPIC). PLoS One. 7(6):e39361. doi: 10.1371/journal. pone.0039361, 10 pages

979. Müller, D. W. and Bosserhoff, A. K. 2008. Integrin beta 3 expression is regulated by let-7a miRNA in malignant melanoma. Oncogene. 27(52): 6698-706

980. Munoz-Martinez, F., Lu, P., Cortes-Selva, F., Perez-Victoria, J. M., Jimenez, I. A., Ravelo, A. G., Sharom, F. J., Gamarro, F. and Castanys, S. 2004. Celastraceae sesquiterpenes as a new class of

modulators that bind specifically to human P-glycoprotein and reverse cellular multidrug resistance. Cancer Research. 64(19): 7130-7138

981. Murakami, Y., Kawata, A., Seki, Y., Koh, T., Yuhara, K., Maruyama, T., Machino, M., Ho, S., Kadoma, Y. and Fujisawa, S. 2012. Comparative inhibitory effects of magnolol, honokiol, eugenol and bis-eugenol on cyclooxygenase-2 expression and nuclear factor-kappa β activation in RAW264.7 macrophage-like cells stimulated with fimbriae of porphyromonas gingivalis. In vivo. 26(6): 941-50

982. Mure, K. and Rossman, T. G. 2001. Reduction of spontaneous mutagenesis in mismatch repair-deficient and proficient cells by dietary antioxidants. Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis. 480-481: 85-95, https://doi.org/10.1016/S0027-5107(01)00172-5

983. Murillo, G., Peng, X., Torres, K. E. O. and Mehta, R. G. 2009. Deguelin inhibits growth of breast cancer cells by modulating the expression of key members of the Wnt signaling pathway. Cancer Prevention Research. 2(11): 942-950

984. Mustacich, D. J., Leonard, S. W., Devereaux, M. W., Sokol, J. R. and Traber, M. G. 2006. α-Tocopherol regulation of hepatic cytochrome P450s and ABC transporters in rats. Free Radical Biology and Medicine. 41(7): 1069-1078

985. Nadiminty, N., Tummala, R., Lou, W., Zhu, Y., Shi, X. B., Zou, J. X., Chen, H., Zhang, J., Chen, X., Luo, J., deVere, W. RW., Kung, H. J., Evans, C. P. and Gao, A. C. 2012. MicroRNA let-7c is downregulated in prostate cancer and suppresses prostate cancer growth. Plos One. 7(3): e32832, doi: 10.1371/journal.pone.0032832, 10 pages

986. Nagineni, C. N., Raju, R., Nagineni, K. K., Kommineni, V. K., Cherukuri, A., Kutty, R. K., Hooks, J. J. and Detrick, B. 2014. Resveratrol suppresses expression of VEGF by human retinal pigment epithelial cells: Potential nutraceutical for age-related macular degeneration. Aging Dis. 5(2): 88-100

987. Nakagawa-Goto, K., Chen, J., Cheng, Y., Lee, W., Takeya, M., Saito, Y., Lee, K. and Shyur, L. 2016. Novel sesquiterpene

lactone analogues as potent anti-breast cancer agents. Molecular Oncology. 10(6): 921-937

988. Nakai, R., Iida, S., Takahashi, T., Tsujita, T., Okamoto, S., Takada, C., Akasaka, K., Ichikawa, S., Ishida, H., Kusaka, H., Akinaga, S., Murakata, C., Honda, S., Nitta, M., Saya, H. and Yamashita, Y. 2009. K858, a novel inhibitor of mitotic kinesin E95 and antitumor agent induces cell death in cancer cells. Cancer Res. 69(9): 3901-9

989. Nakakida, M., Deng, Z., Suzuki, T., Dohmae, N., Nakamura, Y. and Hamamoto, R. 2015. PRMT6 increases cytoplasmic localization of p21CDKN1A in cancer cells through arginine methylation and makes more resistant to cytotoxic agents. Oncotarget. 6(31): 30957-30967

990. Nakamura, H., Kumei, Y., Morita, S., Shimokawa, H., Ohya, K. and Shinomiya, K. 2003. Antagonism between apoptotic (Bax/Bcl-2) and anti-apoptotic (IAP) signals in human osteoblastic cells under vector-averaged gravity condition. Ann N Y Acad Sci. 1010:143-7, https://doi.org/10.1196/annals.1299.023

991. Nakamura, Y., Oka, M., Soda, H., Shiozawa, K., Yoshikawa, M., Itoh, A., Ikegami, Y., Tsurutani, J., Nakatomi, K., Kitazaki, T., Doi, S., Yoshida, H. and Kohno, S. 2005. Gefitinib ('Iressa', ZD1839), an epidermal growth factor receptor tyrosine kinase inhibitor, reverses breast cancer resistance protein ABCG2-mediated drug resistance. Cancer Res. 65(4): 1541-1546

992. Nakano, K. and Vousden, K. H. 2001. PUMA, a novel proapoptotic gene, is induced by p53. Molecular Cell. 7(3): 683-694

993. Nakayama, A., Takagi, S., Yusa, T., Yaguchi, M., Hayashi, A., Tamura, T., Kawakita, Y., Ishikawa, T. and Ohta, Y. 2013. Antitumor activity of TAK-285, an investigational, non-Pgp substrate Her2/Egfr kinase inhibitor, in cultured tumor cells, mouse and rat xenograft tumors, and in an Her2-positive brain metastasis model. J Cancer. 4(7): 557-565

994. Nappi, A. J. and Vass, E. 1998. Hydroxyl radical formation via iron-mediated Fenton chemistry is inhibited by methylated catechols. Biochim Biophys Acta. 1425(1): 159-67

995. Nappo, G., Handle, F., Santer, F. R., McNeill, R. V., Seed, R. I., Collins, A. T., Morrone, G., Culig, Z., Maitland, N. J. and Erb, H. H. H. 2017. The immunosuppressive cytokine interleukin-4 increases the clonogenic potential of prostate stem-like cell by activation of STAT6 signalling. Oncogenesis. 6: e342, doi: 10.1038/oncsis.2017.e3, 12 pages

996. Nascimento, M. A. D., Lira, F. D. S., Punaro, G. R., Mello, M. T., Tufik, S. and Higa, E. M. S. 2017. Short-term I-arginine supplementation attenuates elevation of interleukin 6 level after resistance exercise in overweight men. Clin Nutr ESPEN. 22: 43-47, doi: 10.1016 / j.clnesp. 2017.09.001

997. Nasu, Y., Nishida, K., Miyazawa, S., Komiyama, T., Kadota, Y., Abe, N., Yoshida, A., Hirohata, S., Ohtsuka, A. and Ozaki, T. 2008. Trichostatin A, a histone deacetylase inhibitor, suppresses synovial inflammation and subsequent cartilage destruction in a collogen antibody-induced arthritis mouse model. Osteoarthritis Cartilage. 16(6): 723-32

998. Natsume, Y., Ito, S., Satsu, H. and Shimizu, M. 2009. Protective effect of quercetin on ER stress caused by calcium dynamics dysregulation in intestinal epithelial cells. Toxicology. 258(2-3):164-175, https://doi.org/10.1016/j.tox.2009.01.021

999. Navarro, M. D. 1959. Five years experience with laetrile therapy in advanced cancer. Acta Unio Int Contra Cancrum. 15(Suppl 1): 209-21

1000. Nechuta, S., Lu, W., Chen, Z., Zheng, Y., Gu, K., Cai, H., Zheng, W. and Shu, X. O. 2011. Vitamin supplement use during breast cancer treatment and survival: a prospective cohort study. Cancer Epidemiol Biomarkers Prev. 20(2):262-271

1001. Nechuta, S., Shu, X., Li, H., Yang, G., Ji, B., Xiang, Y., Cai, H., Chow, W., Gao, Y. and Zheng, W. 2012. Prospective cohort study of tea consumption and risk of digestive system cancers: results from the Shanghai women's health study. Am J Clin Nutr. 96(5): 1056-1063

1002. Nelson, E. A., Walker, S. R., Kepich, A., Gashin, L. B., Hideshima, T., Ikeda, H., Chauhan, D., Anderson, K. C. and

Frank, D. A. 2008. Nifuroxazide inhibits survival of multiple myeloma cells by directly inhibiting STAT3. 112(13): 5095-102

1003. Neto, C. C. 2007. Cranberry and its phytochemicals: A review of in vitro anticancer studies. J Nutr. 137(1): 1865-1935, doi: 10.1093/jn/1371.186S

1004. Netsch, M. I., Gutmann, H., Aydogan, C. and Drewe, J. 2006. Green tea extract induces interleukin-8 (IL-8) mRNA and protein expression but specifically inhibits IL-8 secretion in Caco-2 cells. Planta Med. 72(8): 697-702

1005. Nguyen, L. T., Lee, Y., Sharma, A. R., Park, J., Jagga, S., Sharma, G., Lee, S. and Nam, J. 2017. Quercetin induces apoptosis and cell cycle arrest in triple-negative breast cancer cells through modulation of Foxo3a activity. Korean J Physiol Pharmacol. 21(2): 208-213

1006. Nguyen, T. K. and Grant, S. 2014. Dinaciclib (SCH727965) inhibits the unfolded protein response through a CDK1-and 5-dependent mechanism. Mol Cancer Ther. 13(3): OF1-OF13, doi: 10.1158/1535-7163.MCT-13-0714

1007. Nicolai, E., Sinibaldi, F., Sannino, G., Lagana, G., Basoli, F., Licoccia, S., Cozza, P., Santucci, R. and Piro, M. C. 2017. Omega-3 and Omega-6 fatty acids act as inhibitors of the matrix metalloproteinase-2 and matrix metalloproteinase-9 activity. The Protein Journal. 36(4): 278-285

1008. Nielsen, V. G., Lemole, G. M. Jr., Natika, R. W., Weinand, M. E., Hussaini, S., Baaj, A. A. and Steinbrenner, E. B. 2014. Brain tumors enhance plasmatic coagulation: the role of hemeoxygenase-1. Anesth Analg. 118(5): 919-24

1009. Niemeyer, H. B., Honig, D. M., Kulling, S. E. and Metzler, M. 2003. Studies on the metaboılism of the plant lignans secoisolariciresinol and matairesinol. J Agric Food Chem. 51(21): 6317-25

1010. Nishimuro, H., Ohnishi, H., Sato, M., Ohnishi-Kameyama, M., Matsunaga, I., Naito, S., Ippoushi, K., Oike, H., Nagata, T., Akasaka, H., Saitoh, S., Shimamoto, K. and Kobori, M. 2015. Estimated daily intake and seasonal food sources of quercetin in Japan. Nutrients. 7(4): 2045-2358

1011. Nkondjock, A., Shatenstein, B., Maisonneuve, P. and Ghadirian, P. 2003. Specific fatty acids and human colorectal cancer: an overview. Cancer Detection and Prevention. 27(1): 55–66, PMID: 12600418

1012. Nkosi, C. Z., Opoku, A. R. and Terblanche, S. E. 2006. Antioxidative effects of pumpkin seed (*Cucurbita pepo*) protein isolate in CCl4-induced liver injury in low-protein fed rats. Phytother Res. 20(11):935-40

1013. No, J. H., Kim, Y. and Song, Y. S. 2014. Targeting Nrf2 signaling to combat chemoresistance. Journal of Cancer Prevention. 19(2): 111-117

1014. Nobta, M., Tsukazaki, T., Shibata, Y., Xin, C., Moriishi, T., Sakano, S., Shindo, H. and Yamaguchi, A. 2005. Critical regulation of bone morphogenetic protein-induced osteoblastic differentiation by Delta1/Jagged1-activated notch1 signaling. J Biol Chem. 280(16): 15842-8

1015. Nonn, L., Peng, L., Feldman, D. and Peehl, M. D. 2006. Inhibition of p38 by vitamin D reduces interleukin-6 production in normal prostate cells via mitogen-activated protein kinase phosphatase 5: Implications for prostate cancer prevention by vitamin D. Cancer Research. 66(8): 4516-4524

1016. Nöthlings, U., Murphy, P. S., Wilkens, R. L., Henderson, E. B. and Kolonel, N. L. 2007. Flavonols and pancreatic cancer risk. The multiethnic cohort study. Am J Epidemiol. 166(8): 924-931

1017. Nozaki, S., Sissons, S., Chien, D. S. and Sledge, G. W. Jr. 2003. Activity of biphenyl matrix metalloproteinase inhibitor BAY 12-9566 in a human breast cancer orthotopic model. Clin Exp Metastasis. Clin Exp Metastasis. 20(5): 407-12

1018. Nusse, R. and Clevers, H. 2017. Wnt/β-catenin signaling, disease, and emerging therapeutic modalities. Cell. 169(6): 985-999

1019. Nüsslein-Volhard, C. and Wieschaus, E. 1990. Mutations affecting segment number and polarity in Drosophila. Nature. 287(5785): 795-801

1020. Nutritiondata.2018. https://nutritiondata.self.com/foods-0110110100090000000

1021. Nyfeler, B., Chen, Y., Li, X., Pinzon-Ortiz, M., Wang, Z., Reddy, A., Pradhan, E., Das, R., Lehar, J., Schlegel, R., Finan, P. M., Cao, Z. A., Murphy, L. O. and Huang, A. 2012. RAD001 enhances the potency of BEZ235 to inhibit mTOR signaling and tumor growth. Plos One. 7(11): e48548, doi: 10.1371/journal. pone.0048548, 9 pages

1022. O'Donoghue, M. L., Glaser, R., Aylward, P. E., Cavender, M. A., Crisp, A., Fox, K. A., Laws, I., Lopez-Sendon, J. L., Steg, P. G., Theroux, P., Sabatine, M. S. and Morrow, D. A. 2015. Rationale and design of the Losmapimod to inhibit p38 MAPkinase as a therapeutic target and modify outcomes after an acute coronary syndromE trial. Am Heart J. 169(5): 622-630

1023. Obermann-Borst, S. A., Isaacs, A., Younes, Z., van Schaik, R. H. N., van der Heiden, I. P., van Duyn, C. M., Steegers, E. A. P. and Steegers-Theunissen, R. P. M. 2011. General maternal medication use, folic acid, the MDR1C3435T polymorphism, and the risk of a child with a congenital heart defect. American Journal of Obstetrics and Gynecology. 204(3): 236.e1-236.e8, https:// doi.org/10.1016/ j.ajog.2010.10.911

1024. Obermüller-Jevic, U. C., Schlegel, B., Flaccus, A. and Biesalski, H. K. 2001. The effect of β-carotene on the expression of interleukin-6 and heme oxygenase-1 in UV-radiated human skin fibroblasts in vitro. FEBS Letters. 509(2): 186-190

1025. Ogrunch, M., Micco, R. Di., Liontos, M., Bombardelli, L., Mione, M., Fumagalli, M., Gorgoulis, V. G. and di Fagagna, F. 2014. Oncogene-induced reactive oxygen species fuel hyperproliferation and DNA damage response activation. Cell Death and Differentiation. 21(6): 998-1012

1026. Ogunbinu, A. O., Ogunwande, I. A., Essien, E., Cioni, P. L. and Flamini, G. 2007. Sesquiterpenes-rich essential oils of *Polyalthia longifolia Thw.* (*Annonaceae*) from Nigeria. J. Essent Oil Res. 19: 419-421, https://doi.org/10.1080/10412905.2007.9699941

1027. Oh, D. Y., Lee, K. W., Cho, J. Y., Kang, W. K., Im, S. A., Kim, J. W. and Bang, Y. J. 2016. Phase II trial of dacomitinib in patients with Her2-positive gastric cancer. Gastric Cancer. 19(4): 1095-103

1028. Oh, S., Gwak, J., Park, S. and Yang, C. S. 2014. Green tea polyphenol EGCG suppresses Wnt/B-catenin signaling by promoting GSK-3β-and PP2A-independent β-catenin phosphorylation/degradation. Biofactors. 40(6): 586-595
1029. Ohm, J. E., Gabrilovich, D. I., Sempowski, G. D., Kisseleva, E., Parman, K. S., Nadaf, S. and Carbone, D. P. 2003. VEGF inhibits T-cell development and may contribute to tumor-induced immune suppression. Blood. 101(12): 4878-86
1030. Ohm, J.E., Gabrilovich, D.I., Sempowski, G.D., Kisseleva, E., Parman, K.S., Nadaf, S.and Carbone, D.P. 2003 VEGF inhibits T-cell development and may contribute to tumor-induced immune suppression. Blood. 101(12):4878-86.
1031. Ohno, M., Shibata, C., Kishikawa, T., Yoshikawa, T., Takata, A., Kojima, K., Akanuma, M., Kang, J. Y., Yoshida, H., Otsuka, M. and Koike, K. 2013. The flavonoid apigenin improves glucose tolerance through inhibition of microRNA maturation in miRNA103 transgenic mice. Sci Rep. 3:2553, doi: 10.1038/ srep02553, 7 pages
1032. Okawa, Y., Hideshima, T., Steed, P., Vallet, S., Hall, S., Huang, K., Rice, J., Barabasz, A., Foley, B., Ikeda, H., Raje, N., Kızıltepe, T., Yasui, H., Enatsu, S. and Anderson, K. C. 2009. SNX-2112, a selective Hsp90 inhibitor, potently inhibits tumor cell growth, angiogenesis, and osteoclastogenesis in multiple myeloma and other hematologic tumors by abrogating signaling via Akt and ERK. Blood. 113(4): 846-855
1033. Olayanju, A., Copple, I. M., Bryan, H. K., Edge, G. T., Sison, R. L., Wong, M. W., Lai, Z. Q., Lin, Z. X., Dunn, K., Sanderson, C. M., Alghanem, A. F., Cross, M. J., Ellis, E. C., Ingelman-Sundberg, M., Malik, H. Z., Kitteringham, N. R., Goldring, C. E. and Park, B. K. 2015. Brusatol provokes a rapid and transient inhibition of Nrf2 signaling and sensitizes mammalian cells to chemical toxicity-implications for therapeutic targeting of nrf2. Free Radic Biol Med. 78: 202-12, doi: 10.1016/j.freeradbiomed.2014.11.003
1034. Olson, M. J. and Hallahan, R. A. 2004. P38 MAP kinase: a convergence point in cancer therapy. Trends in Molecular Medicine. 10(3): 125-129

1035. Omenn, S. G., Goodman, E. G., Thornquist, D. M., Balmes, J., Cullen, R. M., Glass, A., Keogh, P. J., Meyskens, L. F., Valanis, B., Williams, H. J., Barnhart, S., Cherniack, G. M., Brodkin, A. C. and Hammar, S. 1996. Risk factors for lung cancer and for intervention effects in CARET, the beta-carotene and retinol efficacy trial. J Natl Cancer Inst. 88(21):1550-1559

1036. Oommen, S., Gupta, S. K. and Vlahakis, N. E. 2011. Vascular endothelial growth factor A (VEGF-A) induces endothelial and cancer cell migration through direct binding to integrin α9β1. The Journal of Biological Chemistry. 286(2): 1083-1092

1037. Oosterbaan, A. M., Steegers, E. A. and Ursem, N. T. 2012. The effects of homocyteine and folic acid on angiogenesis and VRGF expression during chicken vascular development. Microvasc Res. 83(2): 98-104

1038. Otte, J. M., Mahjurian-Namari, R., Brand, S., Werner, I., Schmidt, W. E. and Schmitz, E. 2009. Probiotics regulate the expression of COX-2 in intestinal epithelial cells. Nutr Canc. 61(1): 103-13, doi: 10.1080/01635580802372625

1039. Ovejera, A. A., Houchens, D. P., Barker, A. D. and Venditti, J. M. 1978. Inactivity of DL-amygdalin against human breast and colon tumor xenografts in athymic (nude) mice. Cancer Treat Rep. 62(4): 576-8

1040. Paduch, R. and Kandefer-Szerszen, M. 2011. Nitric oxide (NO) and cyclooxygenase-2(COX-2 cross-talk in co-cultures of tumor spheroids with normal cells. Cancer Microenviron. 4(2): 187-198

1041. Pai, G. S., Carneiro, B. A., Mota, J. M., Costa, R., Leite, C. A., Barroso-S, R., Kaplan, J. B., Chae, Y. K. and Giles, F. J. 2017. Wnt/beta-catenin pathway: modulating anticancer immune response. 10:101, doi: 10.1186/s13045-017-0471-6, 12 pages

1042. Paine, A., Eiz-Vesper, B., Blasczyk, R. and Immenschuh, S. 2010. Signaling to heme oxygenase-1 and its anti-inflammatory therapeutic potential. Biochem Pharmacol. 80(12): 1895-903

1043. Pallauf, K., Duckstein, N., Hasler, M., Klotz, L. and Rimbach, G. 2017. Flavonoids as putative inducers of the transcription factors Nrf2, Foxo, and PPARγ. Oxid Med Cell Longev. 2017:4397340, doi:10.1155/2017/4397340, 11 pages

1044. Palmer, R. L. and Kroening, P. M. 1978. Comparison of low dose radiation therapy alone or combined with procarbazine (NSC-77213) for unresectable epidermoid carcinoma of the lung, state T3, N1, N2 or M1. Cancer. 42(2): 424-428

1045. Palozza, P., Colangelo, M., Simone, R., Catalano, A., Boninsegna, A, Lanza, P., Monego, G. ana Ranelletti, F. O. 2010. Lycopene induces cell growth inhibition by altering mevalonate pathway and Ras signaling in cancer cell lines. Carcinogenesis. 31(10): 1813-1821

1046. Palozza, P., Serini, S., Di Nicuola, F., Boninsegna, A., Torsello, A., Maggiano, N., O.Ranelletti, F., Wolf, I. F., Calviello, G. and Cittadini, A. 2004. B-Carotene exacerbates DNA oxidative damage and modifies p53-related pathways of cell proliferation and apoptosis in cultured cells exposed to tobacco smoke condensate. Carcinogenesis. 25(8): 1315-1325

1047. Palozza, P., Serini, S., Maggiano, N., Tringali, G., Navarra, P., Ranelletti, F. O. and Calviello, G. 2005. B-carotene downregulates the steady-state and heregulin-α-induced COX-2 pathways in colon cancer cells. The Journal of Nutrition. 135(1):129-136, doi:10.1093 /jn/135.1.129

1048. Pan, D., Li, N., Liu, Y., Xu, Q., Liu, Q., You, Y., Wei, Z., Jiang, Y., Liu, M., Guo, T., Cai, X., Liu, X., Wang, Q., Liu, M., Lei, X., Zhang, M., Zhao, X. and Lin, C. 2018. Kaempferol inhibits the migration and invasion of rheumatoid arthritis fibroblast-like synoviocytes by blocking activation of the MAPK pathway. International Immunopharmacology. 55:174-182, https://doi.org/10.1016/j.intimp.2017.12.011

1049. Pan, L., Gong, Z., Zhong, Z., Dong, Z., Liu, Q., Le, Y. and Guo, J. 2011. Lin-28 reactivation is required for let-7 repression and proliferation in human small cell lung cancer cells. Mol Cell Biochem. 355(1-2): 257-63

1050. Pan, M., Chang, W., Lin-Shiau, S., Ho, C. and Lin, J. 2001. Induction of apoptosis by Garcinol and curcumin through cytochrome c release and activation of caspases in human leukemia HL-60 cells. Journal of Agricultural and Food Chemistry. 49(3): 1464-1474

1051. Pan, M., Chen, W., Lin-Shiau, S., Ho, C. and Lin, J. 2002. Tangeretin induces cell-cycle G1 arrest through inhibiting cyclin-dependent kinases 2 and 4 activities as well as elevating Cdk inhibitors p21 and p27 in human colorectal carcinoma cells. Carcinogenesis. 23(10): 1677-1684

1052. Pan, Sai. Yi., Zhou, Jia, Gibbons, L., Morrison, H., Wen, Shi. Wu and the Canadian Cancer Registries Epidemiology Research Group (CCRERG).2011. BMC Cancer. 11(372):1-12

1053. Pan, Y. N., Hui, S. W., Tipoe, L. G., Taylor, W. G., Leung, H. Y. R., Lam, K. W., Tsang, T. W. K. and Mak, W. C. J. 2006. Inhibition of pyocyanin-potentiated IL-8 release by steroids in bronchial epithelial cells. Respiratory Medicine. 100(9): 1614-1622

1054. Pan, Z., Zhuang, J., Ji, C., Cai, Z., Liao, W. and Huang, Z. 2018. Curcumin inhibits hepatocellular carcinoma growth by targeting VEGF expression. 15(4): 4821-4826

1055. Pandey, A. K., Bhattacharya, P., Shukla, S. C., Paul, S. and Patnaik, R. 2015. Resveratrol inhibits matrix metalloproteinases to attenuate neuronal damage in cerebral ischemia: a molecular docking study exploring possible neuroprotection. Neural Regen Res. 10(4): 568-575

1056. Panico, A. M., Cardile, V., Avondo, S., Garufi, F., Gentile, B., Puglia, C., Bonina, F., Santagati, N. A. and Ronsisvalle, G. 2006. The in vitro effect of a lyophilized extract of wine obtained from Jacquez grapes on human chondrocytes. Phytomedicine. 13: 522-526, doi: 10.1016/j.phymed.2005.06.009

1057. Panieri, E. and Santoro, M. M. 2016. ROS homeostasis and metabolism: a dangerous liason in cancer cells. Cell Death & Disease. 7: e2253, doi: 10.1038/cddis.2016.105, 12 pages

1058. Panka, J. D., Liu, Q., Geissler, K. A. and Mier, W. J. 2013. Effects of HDM2 antagonism on sunitinib resistance, p53 activation, SDF-1 induction, and tumor infiltration by $CD11b^{+}$/ $Gr\text{-}1^{+}$ myeloid derived suppressor cells. Mol Cancer. 12:17, doi: 10.1186/1476-4598-12-17, 12 pages

1059. Panzella, L. and Napolitano, A. 2017. Natural phenol polymers: Recent advances in food and health applications. Antioxidants. 6:30, 24 pages, doi: 10.3390/antiox6020030

1060. Paoletti, I., De Gregorio, V., Baroni, A., Tufano, A. M., Donnarumma, G. and Perez, J. J. 2013. Amygdalin analogues inhibit IFN-ϒ signaling and reduce the inflammatory response in human epidermal keratinocytes. Inflammation. 36(6): 1316-26
1061. Papandreou, I., Denko, N. C., Olson, M., Melckebeke, H. V., Lust, S., Tam, A., Solow-Cordero, D. E., Bouley, D. M., Offner, F., Niwa, M. and Koong, A. C. 2011. Identification of an Ire1alpha endonuclease specific inhibitor with cytotoxic against human multiple myeloma. Blood. 117(4): 1311-1314
1062. Parajuli, P., Tiwari, R. V. and Sylvester, P. W. 2015. Anticancer effects of ϒ-tocotrienol are associated with a suppression in aerobic glycolysis. Biological and Pharmaceutical Bulletin. 38(9): 1352-1360
1063. Park, C. H., Han, S. E., Nam-Goong, I. S., Kim, Y. I. and Kim, E. S. 2018. Combined effects of baicalein and docetaxel on apoptosis in 8505c anaplastic thyroid cancer cells via downregulation of the ERK and Akt/mTOR pathways. Endocrinol / Metab (Seoul). 33(1): 121-132, doi: 10.3803 / EnM. 2018. 33. 1 . 121
1064. Park, D., Jeong, H., Lee, M. N., Kwon, O., Yang, Y. R., Noh, J., Suh, P., Park, H. and Ryu, S. H. 2017. Resveratrol induces autophagy by directly inhibiting mTOR through ATP competition. Scientific Reports. 6: 21772, doi: 10.1038/ srep21772, 11 pages
1065. Park, G. B., Kim, D., Kim, Y. S., Kim, J. W., Sun, H., Roh, K. H., Yang, J. W. and Hur, D. Y. 2015. Regulation of ADAM10 and ADAM17 by sorafenib inhibits epithelial-to-mesenchymal transition in Epstein-Barr virus-infected retinal pigment epithelial cells. Invest Ophthalmol Vis Sci. 56(9): 5162-73
1066. Park, H. J., Yoon, S. H., Han, L. S., Zheng, L. T., Jung, K. H., Uhm, Y. K., Lee, J. H., Jeong, J. S., Joo, W. S., Yim, S. V., Chung, J. H. and Hong, S. P. 2005. Amygdalin inhibits genes related to cell cycle in SNU-C4 human colon cancer cells. World J Gastroenterol. 11(33): 5156-61
1067. Park, J. S., Kim, D. K., Shin, H. D., Lee, H. J., Jo, H. S., Jeong, J. H., Choi, Y. L., Lee, C. J. and Hwang, S. C. 2016. Apigenin regulates interleukin-1β-induced production of matrix

metalloproteinase both in the knee joint of rat and in primary cultured articular chondrocytes. Biomol Ther. 24(2): 163-70

1068. Park, J., Kwok, S., Lim, M., Kim, E., Ryu, J., Kim, S., Oh, H., Ju, J. H., Park, S., Kim, H. and Cho, M. L. 2014. STA-21, a promising STAT-3 inhibitor that reciprocally regulates Th17 and treg cells, inhibits osteoclastogenesis in mice and humans and alleviates autoimmune inflammation in an experimental model of rheumatoid arthritis. Arthritis and Rheumatology. 66(4): 918-929

1069. Park, M. and Kim, H. 2017. Anti-cancer mechanism of docosahexaenoic acid in pancreatic carcinogenesis: A mini-review. Journal of Cancer Prevention. 22:1-5, http://doi.org/10.15430/JCP.2017, 5 pages

1070. Park, S. Y., Kim, Y. H., Kim, Y. and Lee, S. J. 2012. Aromatic-turmerone attenuates invasion and expression of MMP-9 and COX-2 through inhibition of NF-kB activation in TPA-induced breast cancer cells. J Cell Biochem. 113(12):3653-62

1071. Park, S., Choi, H. and Kim, Y. J. 2013. Inhibition of Isorhamnetin on β-catenin/Tcf signaling and β-catenin-activated melanogenesis. Journal of Basic & Applied Sciences. 9: 401-409, http://dx.doi.org/10.6000/1927-5129.2013.09.51

1072. Park, S., Gong, J., Choi, Y., Kang, M., Kim, Y. and Kang, Y. 2015. Kaempferol inhibits endoplasmic reticulum stress-associated mucus hypersecretion in airway epithnelial cells and ovalbumin-sensitized mice. PlosOne. 10(11): e0143526, doi: 10.1371/journal.pone.0143526, 17 pages

1073. Park, S., Lee, S., Song, S., Heo, D., Park, B., Lee, D., Kim, K. and Sung, M. 2003. The effect of nitric oxide on cyclooxygenase-2 (COX-2) overexpression in head and neck cancer cell lines. Int J Cancer. 107(5): 729-738

1074. Park, S., Lim, W., Bazer, F. W. and Song, G. 2018. Apigenin induces ROS-dependent apoptosis and ER stress in human endometriosis cells. J Cell Physiol. 233: 3055-3065, doi: 10.1002/jcp.26054

1075. Park, S., Murphy, S. P., Wilkens, L. R., Henderson, B. E. and Kolonel, L. N. 2008. Legume and isoflavone intake and prostate

cancer risk: The multiethnic cohort study. International Journal of Cancer. 123(4): 927-932.

1076. Patel, Y., Shah, N., Lee, J. S., Markoutsa, E., Jie, C., Liu, S., Botbyl, R., Reisman, D., Xu, P.and Chen, H. 2016. A novel double-negative feedback loop between miR-489 and HER2-SHP2-MAPK signaling axis regulates breast cancer cell proliferation and tumor growth. Oncotarget. 7(14): 18295-308

1077. Pati, S., Pelser, C. B., Dufraine, J., Bryant, J. L., Reitz, M. S. and Weichold, F. F. 2002. Antitumorigenic effects of HIV protease inhibitor ritonavir: inhibition of Kaposi sarcoma. Blood. 99(10): 3771-3779

1078. Patil, R.H., Babu, R.L., Naveen Kumar, M., Kiran Kumar, K.M., Hegde, S. M., Nagesh, R., Ramesh, G.T.and Sharma, S. C. 2016 Anti-Inflammatory Effect of Apigenin on LPS-Induced Pro-Inflammatory Mediators and AP-1 Factors in Human Lung Epithelial Cells. Inflammation. 39(1):138-147. doi: 10.1007/s10753-015-0232-z.

1079. Patnaik, A., Haluska, P., Tolcher, W. A., Erlichman, C., Papadopoulos, P. K., Lensing, L. J., Beeram, M., Molina, R. J., Rasco, W. D., Arcos, R. R., Kelly, S. C., Wijayawardana, S. R., Zhang, X., Stancato, F. L., Bell, R., Shi, P., Kulanthaivel, P., Pitou, C., Mulle, B. L., Farrington, D. L., Chan, M. E. and Goetz, P. M. 2016. A first-in-human phase I study of the oral p38 MAPK inhibitor, Ralimetinib (LY2228820 Dimesylate), in patients with advanced cancer. Clinical Cancer Research. 22(5): 1095-1102

1080. Paβlack, N., Doherr, M. G. and Zentek, J. 2016. Effects of free amino acids on cytokine secretion and proliferative activity of feline T cells in an in vitro study using the cell line MYA-1. Cytotechnology. 68(5): 1949-1961

1081. Pegram, M., Hsu, S., Lewis, G., Pietras, R., Beryt, M., Sliwkowski, M., Coombs, D., Baly, D., Kabbinavar, F. and Slamon, D. 1999. Inhibitory effects of combinations of HER-2/neu antibody and chemotherapeutic agents used for treatment of human breast cancers. Oncogene. 18(13): 2241-51

1082. Pellikainen, J. M., Ropponen, K. M., Kataja, V. V., Kellokoski,J. K., Eskelinen, M. J. and Kosma, V. M. 2004. Expression of

matrix metalloproteinase (MMP)-2 and MMP-9 in breast cancer with a special reference to activator protein-2, HER2, and prognosis. Clin Cancer Res. 10(22): 7621-8

1083. Peng, G., Dixon, D. A., Muga, S. J., Smith, T. J. and Wargovich, J. M. 2006. Green tea polyphenol (-)-epigallocatechin-3-gallate inhibits cyclooxygenase-2 expression in colon carcinogenesis. Molecular Carcinogenesis. 45(5): 309-319

1084. Peng, H., Wang, H., Xue, P., Hou, Y., Dong, J., Zhou, T., Qu, W., Peng, S., Li, J., Carmichael, P. L., Nelson, B., Clewell, R., Zhang, Q., Andersen, M. E. and Pi, J. 2016. Suppression of Nrf2-Are activity sensitizes chemotherapeutic agent-induced cytotoxicity in human acute monocytic leukemia cells. Toxicol Appl Pharmacol. 292:1-7, doi: 10.1016/j.taop.2015.12.008

1085. Peng, Y. and Croce, C. M. 2016. The role of microRNAs in human cancer. Signal Transduction and Targeted Therapy. 1: 15004, doi: 10.1038/sigtrans.2015.4, 9 pages

1086. Perchellet, J. P., Perchellet, E. M., Abney, N. L., Zirnstein, J. A. and Belman, S. 1986. Effects of garlic and onion oils on glutathione peroxidase activity, the ratio of reduced/oxidized glutathione and ornithine decorboxylase induction in isolated mouse epidermal cells treated with tumor promoters. Cancer Biochem Biophys. 8(4): 299-312

1087. Pereira, F. G., Marquete, R., Domingos, Li T., Rocha, M. E. N., Ferreira-Pereira, A., Mansus, E. and Moreira, D. L. 2017. Antifungal activities of the essential oil and its fractions rich in sesquiterpenes from leaves of *Casearia sylvestris Sw.* Annals of the Brazilian Academy of Sciences. 89(4): 2817-2824

1088. Perez, M. L., Bernal, A., Martin, N. S., Lorenzo, M., Fernandez-Veledo, S. and Galvez, G. B. 2013. Metabolic rescue of obese adipose-derived stem cells by Lin28/Let7 pathway. Diabetes. 62(7): 2368-2379

1089. Perumalsamy, R. L., Nagala, M. and Sarin, A. 2010. Notch-activated signaling cascade interacts with mitochondrial remodeling proteins to regulate cell survival. Proc Natl Acad Sci USA. 107(15): 6882-6887

1090. Peters, U., Littman, A. J., Kristal, A. R., Patterson, R. E, Potter, J. D.and White, E. 2008. Vitamin E and selenium supplementation and risk of prostate cancer in the vitamins and lifestyle (VITAL) study cohort. Cancer Causes Control. 19(1):75-87, doi:10.1007/s10552-007-9072-y

1091. Pikarsky, E., Porat, R. M., Stein, I., Abramovitch, R., Amit, S., Kasem, S., Gutkovich-Pyest, E., Urieli-Shoval, S., Galun, E. and Ben-Neriah, Y. 2004. NF-kappaB functions as a tumour promoter in inflammation-associated cancer. Nature. 431(7007): 461-6

1092. Ping, J., Li, J. T., Liao, Z.X., Shang, L.and Wang, H. 2011. Indole-3-carbinol inhibits hepatic stellate cells proliferation by blocking NADPH oxidase/reactive oxygen species/p38 MAPK pathway. Eur J Pharmacol. 650(2-3):656-62.

1093. Pinnix, C. C. and Herlyn, M. 2007. The many faces of Notch signaling in skin-derived cells. Pigment Cel Res. 20(6): 458-65

1094. Pirnia, F., Schneider, E., Betticher, D. C. and Borner, M. M. 2002. Mitomycin c induces apoptosis and caspase-8 and -9 processing through a caspase-3 and Fas-independent pathway. Cell Death Differ. 9(9): 905-14

1095. Pizato, N., Luzete, B. C., Kiffer, L. F. M. V., Correa, L. H., Santos, I., Assumpçao, J. A. F., Ho, M. K. and Magalhaes, K. G. 2018. Omega-3 docosahexaenoic acid induces pyroptosis cell death in triple-negative breast cancer cells. Scientific Reports. 8: 1952, doi: 10.1038/s41598-018-20422-0, 12 pages

1096. Plenchette, S., Cheung, H. H., Fong, W. G., LaCasse, E. C. and Korneluk, R. G. 2007. The role of XAF1 in cancer. Curr Opin Investig Drugs. 8(6): 469-76

1097. Plumb, G. W., Price, K. R. and Williamson, G. 1999. Antioxidant properties of flavonol glycosides from green beans. Redox Rep. 4(3): 123-7

1098. Pobezinsky, A. L., Etzensperger, R., Jeurling, S., Alag, A., Kadakia, T., McCaughtry, M. T., Kimura, Y. M., Sharrow, O. S., Guinter, I. T.ç, Feigenbaum, L. and Singer, A. 2015. Let-7 miRNAs target the lineage-specific transcription factor PLZF to regulate terminal NKT cell differentiation and effector function. Nat Immunol. 16(5): 517-524

1099. Pollock, L. R. 2016. The effect of green leafy and cruciferous vegetable intake on the incidence of cardiovascular disease: A meta-analysis. JRSM Cardiovasc Dis.5:1-9, doi: 10.1177 / 2048004016661435

1100. Poor Feyzi, A. A., Hagh, M. F., Ebadi, T., Asanjan, K. S., Akbari, A. M., Talebi, M. and Emadi, B. 2015. The effect of resveratrol on the expression of MDR1 gene in leukemic lymphoblast's of acute lymphoblastic leukemia patients. Caspian J Intern Med. 6(2): 113-115

1101. Porta, C., Paglino, C. and Mosca, A. 2014. Targeting PI3K/ Akt/mTOR signaling in cancer. Front Oncol. 4:64, doi:10.3389/ fonc.2014.00064, 11 pages

1102. Pot, K. G., Geelen, A., van Heijningen, E. B.,Siezen, C. L. E., van Kranen, H. J.and Kampman, E. 2008. Opposing associations of serum n-3 and n-6 polyunsaturated fatty acids with colorectal adenoma risk: An endoscopy-based case–control study. Int J Cancer. 123(8):1974-1977

1103. Preet, R., Mohapatra, P., Das, D., Satapathy, S. R., Choudhuri, T., Wyatt, D. M. and Kundu, C. N. 2013. Lycopene synergistically enhances quinacrine action to inhibit Wnt-TCF signaling in breast cancer cells through APC. Carcinogenesis. 34(2): 277-286

1104. Previte, D. M. and Piganelli, J. D. 2018. Reactive oxygen species and their implications on CD4+ T cells in type 1 diabetes. Antioxid Redox Signal. 29(14): 1414

1105. Pross, C., Faroog, M. M., Angle, N., Lane, J. S., Cerveira, J. J., Xavier, A. E., Freischlag, J. A., Law, R. E. and Gelabert, H. A. 2002. Dexamethasone inhinits vascular smooth muscle cell migration via modulation of matrix metalloproteinase activity. J Surg Res. 102(2): 57-62

1106. Proto, M. C., Fiore, D., Piscopo, C., Franceschelli, S., Bizzarro, V., Laezza, C., Lauro, G., Feoli, A., Tosco, A., Bifulco, G., Sbardella, G., Bifulco, M. and Gazzerro, P. 2017. Inhibition of Wnt/β-catenin pathway and histone acetyltransferase activity by Rimonabant: a therapeutic target for colon cancer. Scientific Reports. 7: 11678, doi: 10.1038/s41598-11688-x, 14 pages

1107. Purow, B. 2012. Notch inhibition as a promising new approach to cancer therapy. Adv Exp Med Biol. 727: 305-19, doi: 10.1007/978-1-4614-0899-4_23
1108. Pyne, N. J., El Buri, A., Adams, D. R. and Pyne, S. 2018. Sphingosine 1-phosphate and cancer. Adv Biol Regul. 68: 97-106, doi: 10.1016/j.jbior.2017.09.006
1109. Qian, L., Xie, B., Wang, Y. and Qian, J. 2015. Amygdalin-mediated inhibition of non-small cell lung cancer cell invasion in vitro. Int J Clin Exp Pathol. 8(5): 5363-5370
1110. Qin, B., Liu, J., Liu, S., Li, B. and Ren, J. 2016. Kaempferol targets estrogen-related receptor α and inhibits cell proliferation and invasion in retinoblastoma via Wnt/β-catenin signaling pathway. Int J Clin Exp Med. 9(11): 21415-21423
1111. Qin, R., Zhou, J., Chen, C., Xu, T., Yan, Y., Ma, Y., Zheng, Z., Shen, Y., Lu, Y., Fu, D. and Chen, J. 2014. LIN28 is involved in glioma carcinogenesis and predicts outcomes of glioblastoma multiforme patients. Plos One. 9(1): e86446, doi: 10.1371/journal.pone.0086446, 11 pages
1112. Qu, Y., Olsen, J. R., Yuan, X., Cheng, P. F., Levesgue, M. P., Brokstad, K. A., Hoffman, P. S., Oyan, A. M., Zhang, W., Kalland, K. H. and Ke, X. 2018. Small molecule promotes β-catenin citrullination and inhibits Wnt signaling in cancer. 14(1): 94-101
1113. Quach, H. T., Kondo, T., Watanabe, M., Tamura, R., Yajima, Y., Sayama, S., Ando, M. and Kataoka, T. 2017. Eudesmane-type sesquiterpene lactones inhibit nuclear translocation of the Nuclear Factor kB subunit RelB in response to α lymphotoxin B stimulation. Biol Pharm Bull. 40(10): 1669-1677
1114. Quero, A., Molinie, R., Brancourt, D., Remy, M. J. and Mesnard, F. 2016. Sesquiterpene composition of *Cinnamosma fragrans*: A Malagasy endemic plant used in traditional medicine. Comptes Rendus Chimie. 19(9): 1056-1061
1115. Radjabi, A. R., Sawada, K., Jagadeeswaran, S., Eichbichler, A., Kenny, H. A., Montag, A., Bruno, K. and Lengyel, E. 2008. Thrombin induces tumor invasion through the induction and association of matrix metalloproteinase-9 and β1-integrin on

the cell surface. The Journal of Biological Chemistry. 283(5): 2822-2834

1116. Rahman, S. and Islam, R. 2011. Mammalian Sirtl: insights on its biological functions. Cell Communication and Signaling. 9:11, https://doi.org/10.1186/1478-811x-9-11, 8 pages

1117. Rajapaksha, H. and Forbes, B. E. 2015. Ligand-binding affinity at the insulin receptor isoform-A and subsequent IR-A tyrosine phosphorylation kinetics are important determinants of mitogenic biological outcomes. Front Endocrinol (Lausanne). 6: 107, doi: 10.3389/fendo.2015.00107, 11 pages

1118. Rajendran, P., Li, F., Shanmugam, M. K., Vali, S., Abbasi, T., Kapoor, S., Ahn, K. S., Kumar, A. P. and Sethi, G. 2012. Honokiol inhibits signal transducer and activator of transcription-3 signaling, proliferation and survival of hepatocellular carcinoma cells via the protein tyrosine phosphate SHP-1. J Cell Physiol. 227(5): 2184-95

1119. Ramel, F., Birtic, S., Cuiné, S., Triantaphylidès, C., Ravanat, J. and Michel Havaux. 2012 Chemical Quenching of Singlet Oxygen by Carotenoids in Plants Plant Physiol. 158(3): 1267–1278.

1120. Ramesh, S., Wildey, G. M. and Howe, P. H. 2009. Transforming growth factor β (TGFβ)-induced apoptosis. Cell Cycle. 8(1): 11-17

1121. Ranieri, G., Patruno, R., Ruggieri, E., Montemurro, S., Valerio, P. and Ribatti, D. 2006. Vascular endothelial growth factor (VEGF) as a target of bevacizumab in cancer: from the biology to clinic. Curr Med Chem. 13(16): 1845-57

1122. Ranzato, E., Martinotti, S., Magnelli, V., Murer, B., Biffo, S., Mutti, L. and Burlando, B. 2012. Epigallocatechin-3-gallate induces mesothelioma cell death via H2O2-dependent T-type Ca2+ channel opening. J Cell Mol Med. 16(11): 2667-78

1123. Rapraeger, A. C. 2013. Synstatin: a selective inhibitor of the syndecan-1-coupled IGF1R-αvβ3 integrin complex in tumorigenesis and angiogenesis. FEBS J. 280(10): 2207-15

1124. Rasalkar, D. D., Chu, C. W., Cheung, K., Yeung, K. D., Shi, L., Wang, D., Ng, P. and Ahuja, T. A. 2010. Magnetic resonance

changes with spectroscopy and disffusion tensor imaging after acute cyanide poisoning in a chils. European Journal of Radiology Extra. 73: e5-e8, doi: 10.16/j.ejrex.2009.08.006

1125. Rawangkan, A., Iida, K., Sakai, R., Fujiki, H. and Suganuma, M. 2017. Abstract 2665: Green tea catechin, EGCG, enhances antitumor immunity by down-regulation of PD-L1 expression in non-small human lung cancer cell lines. Proceedings: AACR Annual Meeting 2017; April 1-5, 2017; Wahington, DC, doi: 10.1158/1538-7445. AM2017-266577:13

1126. Reay, P. F. and Lancaster, J. E. 2001. Accumulation of anthocyanins and quercetin glycosides in 'Gala' and 'Royal Gala' apple fruit skin with UV-B-visible irradiation: modifying effects of fruit maturity, fruit side and temperature. Scientia Horticulturae. 90(1-2):57-68

1127. Reedijk, M., Odorcic, S., Chang, L., Zhang, H., Miller, N., McCready, D. R., Lockwood, G. and Egan, S. E. 2005. High-level coexpression of JAG1 and NOTCH1 is observed in human breast cancer and is associated with poor overall survival. Cancer Res. 65(18): 8530-7

1128. Reid, T. M. and Loeb, L. A. 1993. Effect of DNA-repair enzymes on mutagenesis by oxygen free radicals. Mutat Res. 289(2): 181-6

1129. Reitzer, J. L., Wice, M. B. and Kennel, D. 1979. Evidence that glutamine, not sugar, is the major energy source for cultured HeLa cells. The Journal of Biological Chemistry. 254(8): 2669-2676

1130. Relic, B., Zeddou, M., Desoroux, A., Beguin, Y., de Seny, D. and Malaise, M. G. 2009. Genistein induces adipogenesis but inhibits leptin induction in human synovial fibroblasts. Laboratoty Investigation. 89(7): 811-822

1131. Reynaud, D., Pietras, E., Barry-Holson, K., Mir, A., Binnewies, M., Jeanne, M., Sala-Torra, O., Radich, J. P. and Passeque, E. 2011. IL-6 controls leukemic multipotent progenitor cell fate and contributes to chronic myelogenous leukemia development. Cancer Cell. 20(5): 661-73

1132. Rharass, T., Lantow, M., Gbankoto, A., Weiss, D. G., Panakova, D. and Lucas, S. 2017. Ascorbic acid alters cell fate commitment of human neural progenitors in a Wnt/β-catenin/ROS signaling dependent manner. J Biomed Sci. 24:78, doi: 10.1186/s12929-017-0385-1, 16 pages
1133. Rhode, J., Fogoros, S., Zick, S., Wahl, H., Griffith, K. A., Huang, J. and Liu, J. R. 2007. Ginger inhibits cell growth and modulates angiogenic factors in ovarian cancer cells. BMC Complement Altern Med. 7-44, doi: 10.1186/1472-6882-7-44
1134. Ribas, A. and Hu-Lieskovan, S. 2016. What does PD-L1 positive or negative mean? The Journal of Experimental Medicine (JEM). 213(13): 2835-2840
1135. Ricca, A., Biroccio, A., Del Bufalo, D., Mackay, A. R., Santoni, A. and Cippitelli, M. 2000. Bcl-2 over-expression enhances NF-kappaB activity and induces mmp-9 transcription in human MCF7 (ADR) breast-cancer cells. Int J Cancer. 86(2): 188-96
1136. Ricciotti, E., Dovizio, M., Di Francesco, L., Anzellotti, P., Salvatore, T., Di Francesco, A., Sciulli, M. G., Pistritto, G., Monopoli, A. and Patrignani, P. 2010. NCX4040, a nitric oxide-donating aspirin, exerts anti-inflammatory effects through inhibition of I kappa B-alpha degradation in human monocytes. J Immunol. 184(4): 2140-7
1137. Ridnour, A. L., Isenberg, S. J., Espey, G. M., Thomas, D. D., Roberts, D. D. and Wink, A. D. 2005. Nitric oxide regulates angiogenesis through a functional switch involving thrombospondin-1. Proc Natl Acad Sci. USA. 102(37): 13147-13152
1138. Rigalli, J. P., Ciriaci, N., Arias, A., Ceballos, M. P., Villanueva, S. S. M., Luquita, M. G., Mottino, A. D., Ghanem, C. I., Catania, V. A. and Ruiz, M. L. 2015. Regulation of multidrug reistance proteins by genistein in a hepatocarcinoma cell line: Impact on sorafenib cytotoxicity. Plos One. 10(3): e0119502, doi:10.1371/journal.pone.0119502, 19 pages
1139. Rini, B. I. and Small, E. J. 2005. Biology and clinical development of vascular endothelial growth factor-targeted therapy in renal cell carcinoma. J Clin Oncol. 23(5): 1028-43

1140. Roberts, D. D. 1996. Regulation of tumor growth and metastasis by thrombospondin-1. FASEB J. 10(10): 1183-91
1141. Roccaro, A. M., Hideshima, T., Raje, N., Kumar, S., Ishitsuka, K., Yasui, H., Shiraishi, N., Ribatti, D., Nico, B., Vacca, A., Dammacco, F., Richardson, P. G. and Anderson, K. C. 2006. Bortezomib mediates antiangiogenesis in multiple myeloma via direct and indirect effects on endothelial cells. Cancer Res. 66(1): 184-91, doi:10.1158/0008-5472.CAN-05-1195
1142. Rocha, G. da G., Oliveira, R. R., Kaplan, M. A. C. and Gatlass, C. R. 2014. 3β-acetyl tormentic acid reverts MRP1/ABCC1 mediated cancer resistance through modulation of intracellular levels of GSH and inhibition of GST activity. European Journal of Pharmacology. 741:140-149, http://dx.doi.org/10.1016/j.ejphar.2014.07.054
1143. Rodriguez, C., Jacobs, J. E., Mondul, M. A., Calle, E. E., McCullough, L. M. and Thun, J. M. 2004. Vitamin E supplements and risk of prostate cancer in U. S. men. Cancer Epidemiol Biomarkers Prev. 13(3): 378-82
1144. Rohan, E. T., Howe, R. G., Friedenreich, M. C., Jain, M. and Miller, B. A. 1993. Dietary fiber, vitamins A, C, and E, and risk of breats cancer: a cohort study. Cancer Causes and Control. 4(1): 29-37, PMID:8381678
1145. Rohan, E. T., Jain, M., Howe, R. G. and Miller, B. A. 2002. A cohort study of dietary carotenoids and lung cancer risk in women (Canada). Cancer Causes and Control. 13(3): 231-237
1146. Romero, M. M. G., McCathie, G., Jankun, P. and Roehl, H. H. 2018. Damage-induced reactive oxygen species enable zebrafish tail regeneration by repositioning of Hedgehog expressing cells. Native Communications. 9: 4010, doi: 10.1038/s41467-018-06460-2, 11 pages
1147. Rollins, M. R. and Johnson, M. G. R. 2017. CD80 expressed by CD8 +T cells contributes to PD-L1-induced apoptolsis of activated CD8 +T cells. J Immunol Res. 2017: 7659462, doi: 10.1155/2017/7659462, 6 pages
1148. Rosario, F., Nathanielsz, P W., Powell, T. L. and Jansson, T. 2017. Maternal folate deficiency causes inhibition of mTOR

signaling, down-regulation of placental amino acid transporters and fetal growth restriction in mice. Sci Rep. 7: 3982, doi: 10.1038/s41598-017-03888-2, 15 pages

1149. Rosen, N. and She, Q. 2006. Akt and cancer-is it all mTOR?. Cancer Cell. 10(4):254-256

1150. Roskoski, R. 2007. Sunitinib: A VEGF and PDGF receptor protein kinase and angiogenesis inhibitor. Biochemical and Biophysical Research Communications. 356 (2): 323-328

1151. Ross, C. A. 2015. The trophoblast model of cancer. Nutr Cancer. 67(1): 61-7, doi: 10.1080/01635581.2014.956257

1152. Rossi, E., Hung, J., Beilby, J., Knuman, M. W., Divitini, M. L. and Bartholomew, H. 2006. Folate levels and cancer morbidity and mortality: Prospectivecohort study from Busselton, Western Australia. Ann Epidemiol. 16(3):206-212

1153. Rössig, L., Fichtlscherer, B., Breitschopf, K., Haendeler, J., Zeiher, A. M., Mülsch, A. and Dimmeler, S. 1999. Nitric oxide inhibits caspase-3 by S-nitrosation in vivo. J Biol Chem. 274(11): 6823-6

1154. Roswall, N., Olsen, A., Christensen, J., Dragsted, L. O., Overvad, K. and Tjonneland, A. 2010. Source-specific effects of micronutrients in lung cancer prevention. Lung Cancer. 67(3): 275-281

1155. Roudat, H., Traiffort, E, Gorojankina, T., Vincent, L., Faure, H., Schoenfelder, A., Mann, A., Manetti, F., Solinas, A., Taddei, M. and Ruat, M. 2011. Identification and mechanism of action of the acylguanidine MRT-83, a novel potent smoothened antagonist. Mol Pharmacol. 79(3): 453-60

1156. Rowbotham, N. J., Hager-Theodorides, A. L., Cebecauer, M., Shah, D. K., Drakopoulou, E., Dyson, J., Outram, S. V. and Crompton, T. 2007. Activation of the Heggehog signaling pathway in T-lineage cells inhibits TCR repertoire selection in the thymus and peripheral T-cell activation. Blood. 109(9): 3757-3766

1157. Roy, K. R., Reddy, G. V., Maitreyi, L. and Pallu, R. 2009. Celecoxib inhibits MDR1 expression through COX-2-dependent mechanism in human hepatocellular carcinoma (HepG2) cell line. Cancer Chemotherapy and Pharmacology. 65(5): 903-11

1158. Roy, M., Pear, W. S. and Aster, J. C. 2007. The multifaceted role of Notch in cancer. Curr Opin Genet Dev. 17(1): 52-9, doi:10.1016/j.gde.2006.12.001

1159. Roy, S. K., Srivastava, R. K. and Shankar, S. 2010. Inhibition of PI3K/Akt and MAPK/ERK pathways causes activation of Foxo transcription factor, leading to cell cycle arrest and apoptosis in pancreatic cancer. J Mol Signal. 5:10, doi:10.1186/1750-2187-5-10, 13 pages

1160. Roybal, N. C., Yang, S., Sun, C., Hurtado, D., Jagt, D. L. V., Townes, T. M. and Abcouwer, S. F. 2004. Homocyteine increases the expression of vascular endothelial growth factor by a mechanism involving endoplasmic reticulum stress and transcription factor ATF4. 279(15):14853-14859

1161. Rudin, C. M., Hann, C. L., Laterra, J., Yauch, R. L., Callahan, C. A., Fu, L., Holcomb, T., Stinson, J., Gould, S. E., Coleman, B., LoRusso, P. M., von Hoff, D. D., de Sauvage, F. J. and Low, J. A. 2009. Treatment of medulloblastoma with hedgehog pathway inhibitor GDC-0449. N Engl J Med. 361(12): 1173-8

1162. Ruiz-Torres, M. P., Perez-Rivero, G., Diez-Morques, M. L., Griera, M., Ortega, R., Rodriguez-Puyol, M. and Rodriguez-Puyol, D. 2007. Role of activator protein-1 on the effect of arginine-glycine-aspartic acid containing peptides on transforming growth factor β1' promoter activity. The International Journal of Biochemistry & Cell Biology. 39(1): 133-145, doi:10.1016/j.biocel.2006.07.012

1163. Rummel, C., Sachot, C., Poole, S. and Luheshi, G. N. 2006. Circulating interleukin-6 induces fever through a STAT3-linked activation of COX-2 in the brain. Am J Physiol Regul Integr Comp Physiol. 291(5): R1316-26

1164. Russo, M., Milito, A., Spagnuolo, C., Carbone, V., Rosen, A., Minasi, P., Lauria, F. and Russo, L. G. 2017. CK2 and PI3K are direct molecular targets of quercetin in chronic lymphocytic leukemia. Oncotarget. 8(26): 42571-42587

1165. Russo, M., Milito, A., Spagnuolo, C., Carbone, V., Rosen, A., Minasi, P., Lauria, F. and Russo, G. L. 2017. CK2 and PI3K are

direct molecular targets of quercetin in chronic lymphocytic leukemia. Oncotarget. 8(26): 42571-42587

1166. Ryu, K., Lee, B., Lee, I., Oh, S. and Kim, D. 2010. Anti-scratching behavioral effects of N-stearoyl-phytosphingosine and 4-hydroxysphinganine in mice. Lipids. 45(7): 613-618

1167. Ryu, M. J., Cho, M., Song, J. Y., Yun, Y. S., Choi, I. W., Kim, D. E., Park, B. S. and Oh, S. 2008. Natural derivatives of curcumin attenuate the Wnt/beta-catenin pathway through down-regulation of the transcriptional coactivator p300. Biochem Biophys Res Cummun. 377(4): 1304-8

1168. Sachan, R., Kundu, A., Jeon, Y., Choi, W. S., Yoon, K., Kim, I. S., Kwak, J. H. and Kim, H. S. 2018. Afrocyclamin A, a triterpene saponin induces apoptosis and autophagic cell death via the PI3K/Akt/mTOR pathway in human prostate cancer cells. Phytomedicine. 51:139-150, https://doi.org/10.1016/j.phymed.2018.10.012

1169. Safa, M., Jafari, L., Alikarami, F., Shabestari, R. M. and Kazemi, A. 2017. Indole-3-carbinol induces apoptosis of chronic myelogenous leukemia cells through suppression of STAT5 and Akt signaling pathways. Tumour Biol. https://doi.org/10.1177/1010428317705768, 12 pages

1170. Sahoo, M., Ceballos-Olvera, I., del Barrio, L. and Re, F. 2011. Role of the inflammasome, IL-1B, and IL-18 in bacterial infections. Scientific World Journal. 11: 2037-2050, doi: 10.1100/2011/212680

1171. Sahoo, S. K., Sawa, T., Fang, J., Tanaka, S., Miyamoto, Y., Akaike, T. and Maeda, H. 2002. Pegylated zinc protoporphyrin: a water-soluble hem oxygenase inhibitor with tumor-targeting capacity. Bioconjug Chem. 13(5): 1031-8

1172. Saiki, S., Sasazawa, Y., Imamichi, Y., Kawajiri, S., Fuimaki, T., Tanida, I., Kobayashi, H., Sato, F., Sato, S., Ishikawa, K., Imoto, M. and Hattori, N. 2011. Caffeine induces apoptosis, by enhancement of autophagy via PI3K/Akt/mTOR/p70S6K inhibition. Autophagy. 7(2): 176-187

1173. Sain, N., Krishnan, B., Ormerod, M. G., De Rienzo, A., Liu, W. M., Kaye, S. B., Workman, P. and Jackman, A. L. 2006.

Potentiation of paclitaxel activity by the HSP90 inhibitor 17-allylamino-17-demethoxygeldanamycin in human ovarian carcinoma cell lines with high levels of activated AKT. Mol Cancer Ther. 5(5): 1197-208

1174. Saito, S., Furuno, A. Sakurai, J., Sakamoto, A., Park, H., Shin-ya, K., Tsuruo, T. and Tomida, A. 2009. Chemical genomics identifies the unfolded protein response as a target for selective cancer cell killing during glucose deprivation. Cancer Res. 69(10): 4225-4234

1175. Sakla, M. S., Shenouda, N. S., Ansell, P. J., MacDonald, R. S. and Lubahn, D. B. 2007. Genistein affects HER2 protein concentration, activation, and promoter regulation in BT-474 human breast cancer cells. Endocrine. 32(1): 69-78, doi: 10.1007/s12020-007-9006-1

1176. Salas, M., Obando P., Ojeda, L., Ojeda, P., Pérez, A., Vargas-Uribe, M., Rivas, C.I., Vera, J.C.and Reyes, A.M. 2013. Resolution of the direct interaction with and inhibition of the human GLUT1 hexose transporter by resveratrol from its effect on glucose accumulation. Am J Physiol Cell Physiol. 305(1):C90-9, doi: 10.1152/ajpcell.00387.2012

1177. Saleem, M. 2009. Lupeol, a novel anti-inflammatory and anti-cancer dietary trieterpene. Cancer Lett. 285(2): 109-115

1178. Salgia, R. 2009. Role of c-Met in cancer: emphasis on lung cancer. Semin Oncol. 36(2 Suppl 1): S52-S58

1179. Samblas, M., Martinez, A. and Milargo, F. 2018. Folic acid improves the inflammatory response in LPS-activated THP-1 macrophages. Mediators of Inflammation. https: // doi. org/10.1155/2018/ 1312626, Article ID: 1312626, 8 pages

1180. Sampson, V. B., Rong, N. H., Han, J., Yang, Q., Aris, V., Soteropoulos, P., Petrelli, N. J., Dun, S. P. and Krueger, L. J. 2007. MicroRNA let-7a down-regulates MYC and reverts MYC-induced growth in Burkitt lymphoma cells. Cancer Res. 67(20): 9762-70

1181. Samuel, V. T. 2011. Fructose induced lipogenesis: from sugar to fat to insulin resistance. Trends Endocrinol Metab. 22(2): 60-5

1182. Sanderson, S., Valenti, M., Gowan, S., Patterson, L., Ahmad, Z., Workman, P. and Eccles, S. A. 2006. Benzoquinone ansamycin heat shock protein 90 inhibitors modulate multiple functions required for tumor angiogenesis. Mol Cancer Ther. 5(3): 522-32
1183. Santisteban, G. A., Ely, J. T., Hamel, E. E., Read, D. H. and Kozawa, S. W. 1985. Glycemic modulation of tumor tolerance in a mouse model of breast cancer. Biochem Biophys Res Commun. 132(3): 1174-1179
1184. Sarkar, F. H., Rahman, K. M. W. and Li, Y. 2003. Bax translocation to mitochondria is an important event in inducing apoptotic cell death by indol-3-carbinol (I3C) treatment of breast cance cells. The Journal of Nutrition. 133(7): 2434S-2439S
1185. Sasaki, T., Takahashi, S., Uchida, K., Funayama, S., Kainosho, M. and Nakagawa, A. 2006. Biosynthesis of quinolactacin A, a TNF production inhibitor. J Antibot (Tokyo). 59(7): 418-27
1186. Sasazuki, S., Inoue, M., Iwasaki, M., Sawada, N., Shimazu, T., Yamaji, T., Takachi, R., Tsugane, S., Japan Public Health Center–Based Prospective Study Group. 2011. Intake of n-3 and n-6 polyunsaturated fatty acids and development of colorectal cancer by subsite: Japan Public Health Center–based prospective study. Int J Cancer.129(7):1718-29.
1187. Sato, M., Morita, H., Amano, I., Maeda, K., Miyazaki, T., Kambe, F. and Seo, H. 1997. Suppressive effect of quercetin, a bioflavonoid, on TNF-α-mediated stimulation of chemokine expression in cultured human synovial cells. Japanese Journal of Inflammation. 17(4): 383-387
1188. Satoh, M., Takemura, Y., Hamada, H., Sekido, Y. and Kubota, S. 2013. EGCG induces human mesothelioma cell death by inducing reactive oxygen species and autophagy. Cancer Cell International. 13:19. doi: 10.1186/1475-13-19, 8 pages
1189. Satoh, T. and Kaida, D. 2016. Upregulation of p27 cyclin-dependent kinase inhibitor and a C-terminus truncated form of p27 contributes to G1 phase arrest. Scientific Reports. 6: 27829, doi: 10.1038/srep27829, 8 pages
1190. Sawai, M., Ishikawa, Y., Ota, A. and Sakurai, H. 2013. The proto-oncogene JUN is a target of the heat shock transcription

factor HSF1. The FEBS Journal. 280: 6672-6680, doi: 10.1111/febes.12570

1191. Saxton, R. A., Chantranupong, L., Knockenhauer, K. E., Schwartz, T. U. and Sabatini, D. M. 2016. Mechanism of arginine sensing by CASTOR1 upstream of mTORC1. Nature. 536(7615): 229-233

1192. Scalbert, A. and Williamson, G. 2000. Dietary intake and bioavailability of polyphenols. The Journal of Nutrition. 130(8): 2073S-2085S, https://doi.org/10.1093/jn/130.8.2073S

1193. Scales, S. J. and de Sauvage, F. J. 2009. Mechanisms of Hedgehog pathway activation in cancer and implications for therapy. Trends Pharmacol Sci. 30(6): 303-12

1194. Scherbakov, A. M. and Andreeva, O. E. 2015. Apigenin inhibits growth of breast cancer cells: the role of ERα and HER2/neu. Acta Naturae. 7(3):133-139

1195. Schernhammer, E., Wolpin, B., Rifai, N., Cochrane, B., Manson, J. A., Ma, J., Giovannucci, E., Thomson, C., Stampfer, M. J. And Fuchs, C. 2007. Plasma folate, vitamin B_6, vitamin B_{12} and homocyteine and pancreatic cancer risk in four large cohorts. Cancer Res. 67(11):5553-5560

1196. Schmidt, R. L. J., Jutz, S., Goldhahn, K., Witzeneder, N., Gerner, M. C., Trapin, D., Greiner, G., Hoermann, G., Steiner, G., Pickl, W. F., Burgmann, H., Steinberger, P., Ratzinger, F. and Schmetterer, K. G. 2017. Chloroquine inhibits human CD4+ T-cell activation by AP-1 signaling modulation. Scientific Reports. 7: 42191, doi: 10.1038/srep42191, 14 pages

1197. Schmitt, S. M., Stefan, K. and Wiese, M. 2016. Pyrrolopyrimidine derivatives as novel inhibitors of multidrug resistance-associated protein 1 (MRP1, ABCC1). J Med Chem. 59: 3018-3033, doi: 10.1021/acs.jmedchem.5b01644

1198. Schon, M., Bong, A. B., Drewniok, C., Herz, J., Geilen, C. C., Reifenberger, J., Benninghoff, B., Slade, H. B., Gollnick, H. and Schon, M. P. 2003. Tumor-selective induction of apoptosis and the small-molecule immune response modifier Imiquimod. J Natl Cancer Inst. 95(15): 1138-1149

1199. Schuerwegh, A. J., Stevens, W. J., Bridts, C. H. and De Clerck, L. S. 2001. Evaluation of monensin and brefeldin A for flow cytometric determination of interleukin-1 beta, interleukin-6, and tumor necrosis factor-alpha in monocytes. Cytometry. 46(3): 172-6

1200. Schulz, V. 1984. Clinical pharmacokinetics of nitroprusside, cyanide, thiosulphate and thiocyanate. Clin Pharmacokinet. 9(3): 239-51.

1201. Schumacker, P. T. 2006. Reactive oxygen species in cancer cells: Live by the sword, die by the sword. Cancer Cell. 10(3): 241-252

1202. Schust, J., Sperl, B., Hollis, A., Mayer, T. U. and Berg, T. 2006. Stattic: a small-molecule inhibitor of STAT3 activation and dimerization. Chem Biol. 13(11): 1235-42

1203. Schuurman, A. G., Goldbohm, A., Brants, H. A. M. and van den Brandt, P. A. 2002. A prospective cohort study on intake of retinol, vitamin C and E and carotenoids and prostate cancer risk (Netherlands). Cancer causes and Control. 13 (6):573-582

1204. Schuurmans, M. M., Hoffmann, F., Lindberg, R. L. and Meyer, U. A. 2001. Zinc mesoporphyrin represses induced hepatic 5-aminolevulinic acid synthase and reduces heme oxygenase activity in a mouse model of acute hepatic porphyria. Hepatology. 33(5): 1217-22

1205. Scott, P. H. and Lawrence, Jr, J. C. 1998. Attenuation of mammalian target of Rapamycin activity by increased cAMP in 3T3-L1 adipocytes. Journal of Biological Chemistry. 273: 34496-34501, doi: 10.1074/jbc.273.51.34496

1206. Secchiero, P., Corallini, F., di Iasio, M. G., Gonelli, A., Barbarotto, E. and Zauli, G. 2005. TRAIL counteracts the proadhesive activity of inflammatory cytokines in endothelial cells by down-modulating CCL8 and CXCL10 chemokine expression and release. Blood. 105(9): 3413-9

1207. Semba, R. D., Ferrucci, L., Bartali, B., Urpi-Sarda, M., Zamora-Ros, R., Sun, K., Cherubini, A., Bandinelli, S. and Andres-Lacueva, C. 2014. Resveratrol levels and all-cause mortality in older community-dwelling adults. JAMA Intern Med. 174(7): 1077-1084

1208. Seo, H., Ju, J., Jang, K. and Shin, I. 2011. Induction of apoptotic cell death by phyroestrogens by up-regulating the levels of phospho-p53 and p21 in normal and malignant estrogen receptor α-negative breast cells. Nutrition Research. 31(2): 139-146, doi: 10.3892/or.2016.4786

1209. Seo, H., Ku, J. M., Choi, H. S., Wao, J., Lee, B. H., Kim, D. S., Song, H. J., Jang, B., Shin, Y. C. and Ko, S. 2017. Apigenin overcomes drug resistance by blocking the signal transducer and activator of transcription 3 signaling in breast cancer cells. Oncol Rep. 38(2): 715-724

1210. Seo, H., Ku, J. M., Choi, H., Choi, Y. K., Woo, J., Kim, M., Kim, I., Na, C. H., Hur, H., Jang, B., Shin, Y. C. and Ko, S. 2016. Quercetin induces caspase-dependent extrinsic apoptosis through inhibition of signal transducer and activator of transcription 3 signaling in HER2-overexpressing BT-474 breast cancer cells. Oncol Rep. 36(1): 31-42, doi: 10.3892/or.2016.4786

1211. Seo, H., Ku, J. M., Choi, H., Woo, J., Jang, B., Go, H., Shin, Y. C. and Ko, S. 2015. Apigenin induces caspase-dependent apoptosis by inhibiting signal transducer and activator of transcription 3 signaling in HER2-overexpressing SKBR3 breast cancer cells. Molecular Medicine Reports. 12(2): 2977-2984

1212. Seo, H., Ku, J., Choi, H., Woo, J., Jang, B., Shin, Y. and Ko, S. 2014. Induction of caspase-dependent apoptolsis by apigenin by inhibiting STAT3 signaling in HER2-overexpressing MDA-MB-453 breast cancer cells. Anticancer Research. 34(6): 2869-2882

1213. Seo, J. Y., Yu, J.H., Lim, J. W., Mukaida, N. and Kim, H. 2009. Nitric oxide-induced IL-8 expression is mediated by NF-kappaB and AP-1 in gastric epithelial AGS cells. J Physiol Pharmacol. 60(Suppl 7): 101-6

1214. Serini, S., Trombino, S., Oliva, F., Piccioni, E., Monego, G., Resci, F., Boninsegna, A., Picci, N., Ranelletti, F. O. and Calviello, G. 2008. Docosahexaenoic acid induces apoptosis in lung cancer cells by increasing MKP-1 and down-regulating p-ERK1/2 and p-p38 expression. Apoptosis. 13(9):1172-83

1215. Serra, V., Markman, B., Scaltriti, M., Eichhorn, A. J. P., Volero, V., Guzman, M., Botero, L. M., Llonch, E., Altzori, F., Di Cosimo, S., Maira, M., Garcia-Echeverria, C., Parra, L. J., Arribas, J. and Baselga, J. 2008. NVP-BEZ235, a dual PI3K/mTOR inhibitor, prevents PI3K signaling and inhibits the growth of cancer cells with activating PI3K mutations. Cancer Res. 68(19): 8022-30

1216. Serradilla, J. M., Hernandez, A., Lopez-Corrales, M., Ruiz-Moyano, S., Cordoba, de G. M. and Martin, A. 2016. Chapter 6-Composition of the cherry (*Prunus avium L.* and *Prunus cerasus L.; Rosaceae.* Nutritional Composition of Fruit Cultivars. 0:127-147, doi: 10.1016/B978-0-12-408117-8.00006-4

1217. Sesso, D. H., Buring, E. J., Zhang, M. S., Norkus, P. E. and Gaziano, M. J. 2005. Dietary and plasma lycopene and the risk of breast cancer. Cancer Epidemiol Biomarkers Prev. 14(5): 1074-81

1218. Severson, R. K., Nomura, A. M., Grove, J. S. and Stemmermann, G. N. 1989. A prospective study of demographics, diet, and prostate cancer among men of Japanese ancestry in Hawaii. Cancer Res. 49(7): 1857-60

1219. Seyfried, T. N., Sanderson, T. M., El-Abbadi, M. M., McGowan, R. and Mukherjee, P. 2003. Role of glucose and ketone bodies in the metabolic control of experimental brain cancer. Br J Cancer. 89(7): 1375-1382

1220. Shamim, U., Hanif, S., Albanyan, A., Beck, F. W., Bao, B., Wang, Z., Banerjee, S., Sarkar, F. H., Mohammad, R. M., Hadi, S. M. and Azmi, A. S. 2012. Resveratrol-induced apoptosis is enhanced in low pH environments associated with cancer. J Cell Physiol. 227(4):1493-500

1221. Shan, L., Yin, J. and Lu, N. 2013. HER2 expression and relevant clinicopathological features in gastric and gastroesophageal function adenocarcinoma in a Chinese population. Diagn Pathol. 8:76, doi: 10.1186/1746-1596-8-76, 7 pages

1222. Shan, Y. Q., Ying, R. C., Zhou, C. H., Zhu, A. K., Ye, J., Zhu, W., Ju, T. F. and Jin, H. C. 2015. MMP-9 is increased in the pathogenesis of gastric cancer by the mediation of HER2. Cancer Gene Ther. 22(3): 101-7

1223. Shan, Y., Wu, K., Wang, W., Wang, S., Lin, N., Zhao, R., Cassidy, A. and Bao, Y. 2009. Sulforaphane down-regulates COX-2 expression by activating p38 and inhibiting NF-kB-DNA-binding activity in human bladder T24 cells. International Journal of Oncology. 34: 1129-1134, doi: 10.3892/ijo_00000240
1224. Shanahan, F., Niederlehner, A., Carramanzana, N. and Anton, P. 1990. Sulfasalazine inhibits the binding of TNF alpha to its receptor. Immunopharmacology. 20(3): 217-24
1225. Shankar, S. and Lanza, E. 1991. Ditary fiber and cancer prevention. Hematology/Oncology Clinics of North America. 5(1): 25-41, https://doi.org/10.1016/S0889-8588(18)30452-0
1226. Shao, J., Zhang, M., Wang, T., Li, Y. and Wang, C. 2016. The roles of CDR1, CDR2, and MDR1 in kaempferol-induced suppression with fluconazole-resistant *Candida albicans*. Pharmaceutical Biology. 54(6): 984-992
1227. Shapiro, G. I., Bell-McGuinn, K. M., Molina, J. R., Bendell, J., Spicer, J., Kwak, E. L., Pandya, S. S., Millham, R., Borzillo, G., Pierce, K. J., Han, L., Houk, B. E., Gallo, J. D., Alsina, M., Brana, I. and Tabernero, J. 2015. First-in-human study of PF-05212384(PKI-587), a small-molecule, intravenous, dual inhibitor of PI3K and mTOR in patients with advanced cancer. Clin Cancer Res. 21(8): 1888-95
1228. Sharma, A., Belna, J., Espat, J., Rodriguez, G., Cannon, T. V. and Hurteau, J. A. 2009. Effects of omega-3 fatty acids on components of the transforming growth factor beta-1 pathway: implication for dietary modification and prevention in ovarian cancer. American Journal of Obstetrics and Gyneology. 200(5): 516.e1-516.e6
1229. Sharma, A., Gadkari, A. R., Ramakanth, V. S., Padmanabhan, K., Madhumathi, S. D., Devi, L., Appaji, L., Aster, C. J., Rangarajan, A. and Dighe, R. R. 2015. A novel monoclonal antibody against Notch1 targets leukemia-associated mutant Notch1 and depletes therapy. Scientific Reports. 5:11012, doi: 10.1038/srep11012, 19 pages
1230. Sharma, R. and Vinayak, M. 2011. α-tocopherol attenuates NF-kB activation and pro-inflammatory cytokine IL-6 secretion

in cancer-bearing mice. Biosci Rep. 31: 421-428, doi:10.1042/BSR20100137

1231. Sharma, S. L., Chokshi, S. A., Desai, D., Mewada, H. and Singh, A. 2013. Non-enzymatic antioxidants, malondialdehyde and total antioxidant activity as markers of oxidative-stress in arthritis and rheumatoid arthritis. NHL Journal of Medical Sciences. 2(1):57-60

1232. Sharma, S., Salehi, F., Scheithauer, B. W., Rotondo, F., Syro, L. V. and Kovacs, K. 2009. Role of MGMT in tumor development progression, diagnosis, treatment and prognosis. Anticancer Res. 29(10): 3759-68

1233. Sharom, F. J., Yu, X., Liu, R., Chu, J. W., Szabo, K., Müller, M., Hose, C. D., Monks, A., Varadi, A., Seprodi, J. and Sarkadi, B. 1999. Interaction of the P-glycoprotein multidrug transporter (MDR-1) with high affinity peptide chemosensitizers in isolated membranes, reconstituted systems, and intact cells. Biochem Pharmacol. 58(4): 571-86

1234. Shawky, N. M. and Segar, L. 2017. Sulforaphane inhibits platelet-derived growth factor-induced vascular smooth muscle cell proliferation by targeting mTOR/p70S6kinase signaling independent of Nrf2 activation. Pharmacol Res. 119: 251-264, doi: 10.1016/j.phrs.2017.02.010

1235. Shehatou, SG. G. and Suddek, M. G. 2016 Sulforaphane attenuates the development of atherosclerosis and improves endothelial dysfunction in hypercholesterolemic rabbits. Experimental Biology and Medicine. 241: 426-436, doi: 10.1177/1535370215609695

1236. Shen, Q., Uray, I. P., Li, Y., Krisko, T. I., Strecker, T. E., Kim, H. T. and Brown, P. H. 2008. The AP-1 transcription factor regulates breast cancer cell growth via cyclins and E2F factors. Oncogene. 27(3): 366-77

1237. Shen, Y., Lin, C., Chi, W., Wang, C., Hsieh, Y., Wei, Y and Chen, Y. 2013. Resveratrol Impedes the Stemness, Epithelial-Mesenchymal Transition, and Metabolic Reprogramming of Cancer Stem Cells in Nasopharyngeal Carcinoma through

p53 Activation Evid Based Complement Alternat Med. 2013: 590393, doi: 10.1155/2013/590393

1238. Sheptovitsky, Y. G. and Brudviq, G. W. 1986. Isolation and characterization of spinach photosystem II membrane-associated catalase and polyphenol oxidase. Biochemistry. 35(50):16255-63

1239. Shestov, A. A., Liu, X., Ser, Z., Cluntun, A. A., Hung, Y. P., Huang, L., Kim, D., Le, A., Yellen, G., Albeck, J. G. and Locasale, J. W. 2014. Quantitative determinants of aerobic glycolysis identify flux through the enzyme GAPDH as a limiting step. Elife. 3: e03342, doi: 10.7554/eLife.03342, 18 pages.

1240. Shi, J. G., Chen, X., Emm, T., Scherle, P. A., Mcgee, R. and Lo, Y. 2011. The effect of CYP3A4 inhibition or induction on the pharmacokinetics and pharmacodynamics of orally administered ruxolitinib (INCBO18424 phosphate) in healthy volunteers. The Journal of Clinical Pharmacology. 52(6): 809-18

1241. Shi, S., Zhao, X., Liu, B., Li, H., Liu, A., Wu, B., Bi, K. and Jia, Y. 2014. The effects of sesquiterpenes-rich extract of *Alpinia oxyphylla Miq.* on amyloid-β-induced cognitive impairment and neuronal abnormalities in the cortex and hippocampus of mice. Oxidative Medicine and Cellular Longevity. Volume 2014. Article ID451802, http://dx.doi.org/10.1155/2014/451802, 11 pages

1242. Shibata, A., Nakagawa, K., Sookwong, P., Tsuduki, T., Oikawa, S. and Miyazawa, T. 2009. δ-tocotrienol suppresses VEGF induced angiogenesis whereas α-tocopherol does not. J Agric Food Chem. 57: 8696-8704, doi: 10.1021/jf9012899

1243. Shih, L., Lin, Y., Lin, C., Liu, H. and Kao, Y. 2016. Green tea (-)-epigallocatechin gallate induced growth inhibition of human placental choriocarcinoma cells. Placenta. 41:1-9, https://doi.org/10.1016/j. placenta.2016.02.017

1244. Shim, H., Chun, Y. S., Lewis, B. C. and Dang, C. V. 1998. A unique glucose-dependent apoptotic pathway induced by c-Myc. Proc Natl Acad Sci. 95(4): 1511-1516

1245. Shim, M. and Eling, E. T. 2008. Vitamin E succinate induces NAG-1 expression in a p38 kinase dependent mechanism. Molecular Cancer Therapeutics. 7(4): 961-71

1246. Shim, M. S. and Xia, Y. 2013. A reactive oxygen species (ROS)-responsive polymer for safe, efficient and targeted gene delivery in cancer cells. Angew. Chem. Int. Ed. 52(27): 6926-6929
1247. Shimamoto, K., Hayashi, H., Taniai, E., Morita, R., Imaoka, M., Ishii, Y., Suzuki, K., Shibutani, M. and Mitsumori, K. 2011. Antioxidant N-acetyl-L-cysteine (NAC) supplementation residues reactive oxygen species (ROS)-mediated hepatocellular tumor promotion of indol-3-carbinol (I3C) in rats. J Toxicol Sci. 36(6): 775-86
1248. Shin, D. S., Kim, H. N., Shin, K. D., Yoon, Y. J., Kim, S. J., Han, D. C. and Kwon, B. M. 2009. Cryptotan shinone inhibits constituve signal transducer and activator of transcripton 3 function through blocking the dimerization in DU145 prostate cancer cells. Cancer Res. 69(1): 193-202, doi: 10.1158/0008-5472.CAN-08-2575
1249. Shin, J. Y., Lim, J. H. and Park, C. G. 2009. VEGFR1 as a new surface marker for CD4+ regulatory T cells. The Journal of Immunology. 182(1 Supplement)89.41
1250. Shiota, C., Woo, J., Lindner, J., Shelton, D. K. and Magnuson, A. M. 2006. Multiallelic disruption of the rictor gene in mice reveals that mTOR complex 2 is essential for fetal growth and viability. Developmental Cell. 11(4): 583-589
1251. Shklar, G., Schwartz, J., Trickler, D. and Cheverie, S. R. 1993. The effectiveness of a mixture of beta-carotene, alpha-tocopherol, glutathione and ascorbic acid for cancer prevention. Nutr Cancer. 20(2): 145-51
1252. Shoda, H., Yanai, R., Yoshimura, T., Nagai, T., Kimura, K., Sobrin, L., Connor, K. M., Sakoda, Y., Tamada, K., Ikeda, T. and Sonoda, K. 2015. Dietary Omega-3 fatty acids suppress experimental autoimmune uveitis in association with inhibition of Th1 and Th17 cell function. PlosOne. 10(9): e0138241, doi: 10.1371/journal.pone.0138241,13 pages.
1253. Shukitt-Hale, B., Lau, F. C., Carey, A. N., Galli, R. L., Spangler, E. L., Ingram, D. K. and Joseph, J. A. 2008. Blueberry polyphenols attenuate kainic acid-induced decrements in cognition and

alter inflammatory gene expression in rat hippocampus. Nutr Neurosci. 11(4): 172-182

1254. Shukla, S., Bhaskaran, N., Babcook, M. A., Fu, P., MacLenna, G. T. and Gupta, S. 2014. Apigenin inhibits prostate cancer progression in TRAMP mice via targeting PI3K/Akt/Foxo pathway. Carcinogenesis. 35(2): 452-460

1255. Si, H. and Liu, D. 2009. Isoflavone genistein protects human vascular endothelial cells against tumor necrosis factor-α-induced apoptosis through the p38 mitogen-activated protein kinase. Apoptosis. 14(1): 66-76, doi: 10.1007/s10495-008-0283-9

1256. Si, M. S., Reitz, B. A. and Borie, D. C. 2005. Effects of the kinase inhibitor CG41251 (PKC412) on lymphocyte activation and TNF-alpha production. Int Immunopharmacol. 5(7-8): 1141-9

1257. Siddiquee, K., Zhang, S., Guida, W. C., Blaskovich, M. A., Greedy, B., Lawrence, H. R., Yip, M. L. R., Jove, R., McLaughlin, M. M., Lawrence, N. J., Sebti, S. M. and Turkson, J. 2007. Selective chemical probe inhibitor of STAT3, identified through structure-based virtual screening, induces antitumor activity. Proc Natl Acad Sci USA. 104(18): 7391-7396

1258. Siednienko, J., Nowak, J., Moynagh, N. P. and Gorczyca, A. W. 2011. Nitric oxide affects IL-6 expression in human peripheral blood mononuclear cells involving cGMP-dependent modulation of NF-kB activity. Cytokine. 54(3): 282-288

1259. Siegfried, J. M., Gubisch, C. T., Rothstein, M. E., Henry, C. and Stabile, L. P. 2012. Combining the multitargeted tyrosine kinase inhibitor vandetanib with the antiestrogen fulvestrant enhances its antitumor effect in non-small cell lung cancer. J Thorac Oncol. 7(3): 485-95

1260. Simone, R. E., Russo, M., Catalano, A., Monego, G., Froehlich, K., Boehm, V. and Palozza, P. 2011. Lycopene inhibits NF-kβ-mediated IL-8 expression and changes redox and PPARγ signaling in cigarette smoke-stimulated macrophages. Plos One. 6(5): e19652, doi: 10.1371/journal.pone.0019652, 11 pages

1261. Singh, A. R., Joshi, S., Burgoyne, A. M., Sicklich, J. K., Ikeda, S., Kono, Y., Garlich, J. R., Morales, G. A. and Durden, D.

L. 2016. Single agent and synergistic activity of the 'first-in-class' dual PI3K/BRD4 inhibitor SF1126 with sorafenib in hepatocellular carcinoma. Mol Cancer Ther. 15(11): 2553-2562

1262. Singh, A., Singh, A., Sand, J. M. Bauer, S. J., Hafeez, B. B., Meske, L. and Verma, A. K. 2015. Topically applied Hsp90 inhibitor 17AAG inhibits UVR-induced cutaneous squamous cell carcinomas. J Invert dermatol. 135(4): 1098-107

1263. Singh, A., Venkannagari, S., Oh, K. H., Zhang, Y. Q., Rohde, J. M., Liu, L., Nimmagadda, S., Sudini, K., Brimacombe, K. R., Gajghate, S., Ma, J., Wang, A., Xu, X., Shahane, S. A., Xia, M., Woo, J., Mensah, G. A., Wang, Z., Ferrer, M., Gabrielson, E., Li, Z., Rastinejad, F., Shen, M., Boxer, M. B. and Biswal, S. 2016. Small molecule inhibitor of Nrf2 selectively intervenes therapeutic resistance in KEAP1-deficient NSCLC tumors. ACS Chem Biol. 11(11): 3214-3225

1264. Singh, T. and Katiyar, S. K. 2013. Honokiol inhibits non-small cell lung cancer cell migration by targeting PGE2-mediated activation of β-catenin signaling. PlosOne. 8(4): e60749, doi: 10.1371 / journal. pone. 0060749, 12 pages

1265. Singleton, K. D. and Wischmeyer, P. E. 2008. Glutamine attenuates inflammation and NF-kB activation via Cullin-1 deneddylation. Biochem Biophys Res Commun. 373(3): 445-449

1266. Sinno, M., Biagioni, S., Ajmone-Cat, M. A., Pafumi, I., Caramanica, P., Medda, V., Tonti, G., Minghetti, L., Monello, F. and Cacci, E. 2013. The matrix metalloproteinase inhibitor marimastat promotes neural progenitor cell differentiation into neurons by gelatinase-independent TIMP-2-dependent mechanisms. Stem Cells Dev. 22(3): 345-58

1267. Sioulas, V. D., Politi, E., Rizos, D. A., Augoulea, A., Kyroudi, A. and Sergantanis, T. N. 2011. Does hormone therapy, tibolone or raloxifene modify VEGF expression incervical epithelial cells. Climacteric. 15(2): 181-5

1268. Skinner, H. G., Michaud, D. S., Giovannucci, E., Willett, W. C., Colditz, G. A. and Fuchs, C. S. 2006. Vitamin D intake and the risk for pancreatic cancer in two cohort studies. Cancer Epidemiol Biomarkers Prev. 15(9):1688-1695

1269. Skobe, M., Hawighorst, T., Jackson, D. G., Prevo, R., Janes, L., Velasco, P., Riccardi, L., Alitalo, K., Claffey, K. and Detmar, M. 2001. Induction of tumor lymphangiogenesis by VEGF-C promotes breast cancer metastasis. Nature Medicine. 7(2): 192-198

1270. Slusarz, A., Shenouda, N. S., Sakla, M. S., Drenkhahn, S. K., Narula, A. S., MacDonald, R. S., Besch-Williford, C. L. and Lubahn, D. B. 2010. Common botanical compounds inhibit the hedgehog signaling pathway in prostate cancer. Cancer Res. 70(8): 3382-90

1271. Smolarek, A. K., So, J. Y., Burgess, B., Kong, A. T., Reuhl, K., Lin, Y., Shih, W. J., Li, G., Lee, M., Chen, Y., Yang, C. S. and Suh, N. 2012. Dietary administration of δ- and Υ-tocopherol inhibits tumorigenesis in the animal model of estrogen-receptor positive, but not HER-2 breast cancer. Cancer Prev Res (Phila): 5(11): 1310-1320

1272. Sobolewski, C., Cerella, C., Dicato, M., Ghibelli, L. and Diederich, M. 2010. The role of cyclooxygenase-2 in cell proliferation and cell death in human malignancies. International Journal of Cell Biology. 2010: 215158, doi: 10.1155/2010/215158, 21 pages

1273. Soleymaninejad, M., Joursaraei, S. G., Feizi, F. and Anarkooli, I. J. 2017. The effects of lycopene and insulin on histological changes and the expression level of Bcl-2 family genes in the hippocampus of streptozotocin-induced diabetic rats. J Diabetes Res. 2017:4650939, doi:10.1155/2017/4650939, 9 pages

1274. Sommerburg, O., Keunen, J. E. E., Bird, A. C. and van Kuijk, F. J. G. M. 1998. Fruits and vegetables that are sources for lutein and zeaxanthin: the macular pigment in human eyes. Br J Ophthalmol. 82(8): 907-910

1275. Song, H., Bao, J., Wei, Y., Chen, Y., Mao, X., Li, J., Yang, Z. and Xue, Y. 2015. Kaempferol inhibits gastric cancer tumor growth: in vitro and in vivo study. 33(2): 868-874

1276. Song, K., Jing, K., Kim, J., Yun, E., Shin, S., Seo, K., Park, J., Heo, J., Kang, J. X., Suh, K., Wu, T., Park, J., Kweon, G., Yoon, W., Hwang, B. and Lim, K. 2011. Omega-3-polyunsaturated fatty

acids suppress pancreatic cancer cell growth in vitro and in vivo downregulation of Wnt/beta-catenin signaling. Pancreatology. 11: 574-84, doi: 10.1159/000334468

1277. Song, L., Chen, X., Wang, P., Gao, S., Qu, C. and Liu, L. 2018. Effects of baicalein on pancreatic cancer stem cells via modulation of sonic Hedgehog pathway. Acta Biochimica et Biophysica Sinica. ABBS. 50(6): 586-596

1278. Song, W., Dang, Q., Xu, D., Chen, Y., Zhu, G., Wu, K., Zeng, J., Long, Q., Wang, X., He, D. and Li, L. 2014. Kaempferol induces cell cycle arrest and apoptosis in renal cell carcinoma through EGFR/p38 signaling. Oncology Reports. 31(3): 1350-1356

1279. Song, Z. and Xu, X. 2014. Advanced research on anti-tumor effects of amygdalin. Journal of Cancer Research and Therapeutics. 10(5): 3-7

1280. Sorensen, M., Jensen, B. R., Poulsen, H. E., Deng, X., Tyqstrup, N., Dalhoff, K. and Loft, S. 2001. Effects of a Brussels sprouts extract on oxidative DNA damage and metabolising enzymes in rat liver. Food Chem Toxicol. 39(6): 533-40

1281. Soria, J. C., Cortes, J., Massard, C., Armand, J. P., De Andreis, D., Ropert, S., Lopez, E., Catteau, A., James, J., Marier, J. F., Beliveau, M., Martell, R. E. and Baselga, J. 2012. Phase I safety, pharmacokinetic and pharmacodynamic trial of BMS-599626 (AC480), an oral pan-HER receptor tyrosine kinase inhibitor in patients with advanced solid tumors. Ann Oncol. 23(2): 463-71

1282. Sorrenti, V., Guccione, S., Di Giacomo, C., Modica, M. N., Pittala, V., Acquaviva, R., Basile, L., Pappalardo, M. and Salerno, L. 2012. Evaluation of imidazole-based compounds as heme oxygenase-1 inhibitors. Chem Biol Drug Des. 80(6): 876-886

1283. Soto-Cruz, I., Rangel-Corona, R., Valle-Mendiola, A., Moreno-Morales, X., Santiago-Perez, R., Weiss-Steider, B. and Caceres-Cortes, J. R. 2008. The tyrphostin B42 inhibits cell proliferation and Her-2 autophosphorylation in cervical carcinoma cell lines. Cancer Invest. 26(2): 136-44

1284. Sparmann, A. and Bar-Sagi, D. 2004. Ras induced interleukin-8 expression plays a critical role in tumor growth and angiogenesis. Cancer Cell. 6(5): 447-58

1285. Spencer, A., Yoon, S. S., Horrison, S. J., Morris, S. R., Smith, D. A., Brigandi, R. A., Gauvin, J., Kumar, R., Opalinska, J. B. and Chen, C. 2014. The novel AKT inhibitor afuresertib shows favorable safety, pharmacokinetics, and clinical activity in multiple myeloma. Blood. 124(14): 2190-5
1286. Spinelli, J.B., Yoon, H., Ringel, A.E., Jeanfavre, S., Clish, C.B.and Haigis, M.C. Metabolic recycling of ammonia via glutamate dehydrogenase supports breast cancer biomass. Science. 358(6365): 941-946. doi: 10.1126/science.aam9305
1287. Spychalla, J. P. and Desborough, S. L. 1990. Superoxide dismutase, catalse and α-tocopherol content of stored potato tubers. Plant Physiol. 94(3):1214-1218
1288. Sreenivasan, S., Ravichandran, S., Vetrivel, U. and Krishnakumar, S. 2013. Modulation of multidrug resistance 1 expression and function in retinoblastoma cells by curcumin. J Pharmacol Pharmacother. 4(2): 103-109
1289. Stanciu, M., Wang, Y., Kentor, R., Burke, N., Watkins, S., Kress, G., Reynolds, I., Klann, E., Angiolieri, M. R., Johnson, J. W. and DeFranco, D. B. 2000. Persistent activation of ERK contributes to glutamate-induced oxidative toxicity in a neuronal cell line and primary cortical neuron cultures. J Biol Chem. 275(16): 12200-12206
1290. Stanton, R. C. 2012. Glucose-6-phosphate dehydrogenase, NADPH, and cell curvival. IUBMB Life. 64(5): 362-369
1291. Starrett, W. and Blake, D. J. 2011. Sulforaphane inhibits de novo synthesis of IL-8 and MCP-1 in human epithelial cells generated by cigarette smoke extract. Journal of Immunotoxicology. 8(2): 150-158
1292. Stattin, P., Bjor, O., Ferrari, P., Lukanova, A., Lenner, P., Lindahl, B., Hallmans, G. and Kaaks, R. 2007. Prospective study of hyperglycemia and cancer risk. Diabetes Care. 30(3): 561-567
1293. Steinmetz, A. K., Potter, D. J. and Folsom, R. A. 1993. Vegetables, fruit and lung cancer in the Iowa women's healthy study. Cancer Research. 53(3): 536-543

1294. Stenman, U., Alfthan, H. and Hotakainen, K. 2004. Human chorionic gonadotropin in cancer. Clinical Biochemistry. 37(7): 549-561
1295. Stervbo, U., Vang, O. and Bonnesen, O. 2007. A review of the content of the putative chemopreventive phytoalexin resveratrol in red wine. Food Chemistry. 101(2): 449-457
1296. Stevens, V. L., McCullough, M. L., Sun, J., Jacobs, E. J., Campbell, P. T. and Gapstur, S. M. 2011. High levels of folate from supplements and fortification are not associated with increased risk of colorectal cancer. Gastroenterology. 141(1):98-105, doi: 10.1053/j.gastro.2011.04.004.
1297. Stewart, R., Morrow, M., Hammond, S. A., Mulgrew, K., Marcus, D., Poon, E., Watkins, A., Mullins, S., Chodorge, M., Andrews, J., Bannister, D., Dick, E., Crawford, N., Parmentier, J., Alimzhanov, M., Babcook, J. S., Foltz, I. N., Buchanan, A., Bedian, V., Wilkinson, R. W. and McCourt, M. 2015. Identification and characterization of MED14736, an antagonistic anti-PD-L1 monoclonal antibody. Cancer Immunol Res. 3(9): 1052-62
1298. Stivala, L. A., Cazzalini, O. and Prosperi, E. 2012. The cyclin-dependent kinase inhibitor p21CDKN1A as a target of anti-cancer drugs. Curr Cancer Drug Targets. 12(2): 85-96
1299. Stock, C. C., Martin, D. S., Sugiura, K., Fugmann, R. A., Mountain, I. M., Stockert, E., Schmid, F. A. and Tarnowski, G. S. 1978. Antitumor tests of amygdalin in spontaneous animal tumor systems. J Surg Oncol. 10(2): 89-123
1300. Stolzenberg-Solomon, R. Z., Chang, S., Leitzmann, M. F., Johnson, K. A., Johnson, C., Buys, S. S., Hoover, R. N. and Ziegler, R. G. 2006. Folate intake, alcohol use and postmenopausal breast cancer risk in the prostate, lung, colorectal and ovarian cancer screening trial. American Journal of Clinical Nutrition. 83(4):895-904
1301. Stolzenberg-Solomon, Z. R., Sheffler-Collins, S., Weinstein, S., Garabrant, H. D., Mannisto, S., Taylor, P., Virtamo, J. and Albanes, D. 2009. Vitamin E intake, α-tocopherol status, and

pancreatic cancer in a cohort of male smokers. Am J Clin Nutr. 89(2): 584-591

1302. Strandas, C., Kamal-Eldin, A., Andersson, R. and Aman, P. 2008. Phenolic glucosides in bread containing flaxseed. Food Chemistry. 110(4): 997-999

1303. Stricklin, G. P. 1986. Human fibroblast tissue inhibitor of metalloproteinases: glycosylation and function. Coll Relat Res. 6(2): 219-28

1304. Strunz, C. M. C., Roggerio, A., Cruz, P. L., Pacanaro, A. P., Salemi, V. M. C., Benvenuti, L. A., Mansur, A., de Padua. And Irigoyen, M. C. 2017. Down-regulation of fibroblast growth factor 2 and its co-receptors heparin sulfate proteoglycans by resveratrol underlies the improvement of cardiac dysfunction in experimental diabetes. The Journal of Nutritional Biochemistry. 40: 219-227, https://doi.org/10.1016/j.jnutbio.2016.11.015

1305. Su, J. L., Shih, J. Y., Yen, M. L., Jeng, Y. M., Chang, C. C., Hsieh, C. Y., Wei, L. H., Yang, P. C. and Kuo, M. L. 2004. Cyclooxygenase-2 induces EP1-and HER-2/Neu-dependent vascular endothelial growth factor-C up-regulation: a novel mechanism of lymphangiogenesis in lung adenocarcinoma. Cancer Res. 64(2): 554-64

1306. Su, J., Cui, X., Li, Y., Mani, H., Ferreyra, A. G., Danner, L. R., Hsu, L. L., Fitz, Y. and Eichacker, P. Q. 2010. SB203580, a p38 inhibitor, improved cardiac function but worsened lung injury and survival during *Escherichia coli* pneumonia in mice. J Trauma. 68(6): 1317-1327

1307. Su, R., Li, Z., Li, H., Song, H., Bao, C., Wei, J. and Cheng, L. 2010. Grp78 promotes the invasion of hepatocellular carcinoma. BMC Cancer. 10:20, doi: 10.1186/1471-2407-10-20

1308. Subia, B., Chandra, S., Talukdar, S. and Kundu, S. C. 2014. Folate conjugated silk fibroin nanocarriers for targeted drug delivery. Integr Biol (Camb). 6(2): 203-14

1309. Suchard, J. R., Wallace, K. L. and Gerkin, R. D. 1998. Acute cyanide toxicity caused by apricot kernel ingestion. Ann Emerg Med. 32(6): 742-4

1310. Sugimura, K., Miyata, H., Tanaka, K., Hamano, R., Takahashi, T., Kurokawa, Y., Yamasaki, M., Nakajima, K., Takiguchi, S., Mori, M. and Doki, Y. 2012. Let-7 expression is a significant determinant of response to chemotherapy through the regulation of IL-6/STAT3 pathway in esophageal squamous cell carcinoma. Clin Cancer Res. 18(18): 5144-53

1311. Sun, H. N., Kim, S. U., Lee, M. S., Kim, J. M., Yim, M., Yu, D. Y. and Lee, D. S. 2008. Nicotinamide adenine dinucleotide phosphate (NADPH) oxidase-dependent activation of phosphoinositide 3-kinase and p38 mitogen-activated protein kinase signal pathways is required for lipopolysaccharide-induced microglial phagocytosis. Biol Pharm Bull. 31(9): 1711-5

1312. Sun, H., Hu, Y., Gu, Z., Qwens, T. R., Chen, Q. Y. and Edwards, J. I. 2011. Omega-3 fatty acids induce apoptosis in human breast cancer cells and mouse mammary tissue through syndecan-1 inhibition of the MEK-Erk pathway. Carcinogenesis. 32(10): 1518-1524

1313. Sun, L., Chen, W., Qu, L., Wu, J. and Si, J. 2013. Icaritin reverses multidrug resistance of HepG2/ADR human hepatoma cells via downregulation of MDR1 and P-glycoprotein expression. Molecular Medicine Reports. 8(6): 1883-1887

1314. Sun, S., Han, J., Ralph, WM. Jr., Chandrasekaran, A., Liu, K., Auborn, K. J. and Carter, T. H. 2004. Endoplasmic reticulum stress as a correlate of cytotoxicity in human tumor cells exposed to diindolylmethane in vitro. Cell Stress Chaperones. 9(1): 76-87, PMID:15270080

1315. Sun, S., Jia, W., Chen, H., Ma, J., Ge, Y., Yu, J. and Li, J. 2013. Docosahexaenoic acid (DHA) induces apoptosis in human hepatocellular carcinoma cells. Int J Clin Exp Pathol. 6(2): 281-289

1316. Sun, X., Huo, X., Luo, T., Li, M., Yin, Y. and Jiang, Y. 2011. The anticancer flavonoid chrysin induces the unfolded response in hepatoma cells. J Cell Mol Med. 15(11): 2389-2398

1317. Sun, X., Liu, X. and Huang, D. 2013. Curcumin reverses the epithelial-mesenchymal transition of pancreatic cancer cells by inhibiting the Hedgehog signaling pathway. Oncology Reports. 29(6): 2401-2407

1318. Sun, X., Mao, Y., Wang, J., Zu, L., Hao, M., Cheng, G., Qu, Q., Cui, D., Keller, E. T., Chen, X., Shen, K. and Wang, J. 2014. IL-6 secreted by cancer-associated fibroblasts induces tamoxifen resistance in luminal breast cancer. Oncogene. 33: 4450, doi: 10.1038/onc.2014.224

1319. Sun, Y., Lehmbecker, A., Kalkuhl, A., Deschl, U., Sun, W., Rohn, K., Tzvetanova, I. D., Nave, K. A., Baumgartner, W. and Ulrich, R. 2015. STAT3 represents a molecular switch possibly inducing astroglial instead of oligodendroglial differentiation of oligodendroglial progenitor cells in Theiler's murine encephalomyelitis. Neuropathol Appl Neurobiol. 41(3): 347-70

1320. Surai, P. F. 2015. Silymarin as a natural antioxidant: An overview of the current evidence and perspectives. Antioxidants (Basel): 4(1): 204-47, doi: 10.3390/antiox4010204

1321. Suzawa, K., Toyooka, S., Sakaguchi, M., Morita, M., Yamamoto, H., Tomida, S., Ohtsuka, T., Watanabe, M., Hashida, S., Maki, Y., Soh, J., Asano, H., Tsukuda, K. and Miyoshi, S. 2016. Antitumor effect of afatinib, as a human epidermal growth factor receptor 2-targeted therapy, in lung cancers harboring Her2 oncogene alterations. Cancer Sci. 107(1): 45-52, doi: 10.1111/cas.12845

1322. Suzuki, Y., Aoki, K., Saito, H., Umeda, M., Nitta, H., Baron, R. and Ohya, K. 2006. A tumor necrosis factor-alpha antagonist inhibits inflammatory bone respiration induced by *Porphyromonas gingivalis* infection in mice. J Periodontal Res. 41(2): 81-91

1323. Swietach, P., Vaughan-Jones, D. R., Harris, L. A. and Hulikova, A. 2014. The chemistry, physiology and pathology of pH in cancer. Philos Trans R Soc Lond B Biol Sci. 369(1638): 20130099, https:// dx.doi.org/10.1098/rstb.2013.0099, 9 pages

1324. Syrigos, K. N., Rowlinson-Busza, G. and Epenetos, A. A. 1998. In vitro cytotoxicity following specific activation of amygdalin by beta-glucosidase conjugated to a bladder cancer-associated monoclonal antibody. Int J Cancer. 78(6): 712-9

1325. Szatmari, T., Ötvös, R., Hjerpe, A. and Dobra, K. 2015. Syndecan-1 in Cancer: Implications for cell signaling, differentiation and prognostication. Disease Markers. Article ID 796052, 13 pages, http: //dx.doi.org/10.1155/2015/796052

1326. Szeto, Y. T., Tomlinson, B. and Benzie, F. F. I. 2002. Total antioxidant and ascorbic acid content of fresh fruits and vegetables: implications for dietary planning and food preservation. 87(1): 55-59, doi: 10.1079/BJN2001483
1327. Szuster-Ciesielska, A., Plewka, K., Daniluk, J. and Kandefer-Szerszen, M. 2011. Betulin and betulinic acid attenuate ethanol-induced liver stellate cell activation by inhibiting reactive oxygen species (ROS), cytokine (TNF-α, TGF-β) production and by influencing intracellular signaling. Toxicology. 280(3): 152-63
1328. Szylberg, Ł., Karbownik, D. and Marszalek, A. 2016. The role of Foxp3 in human cancers. Anticancer Res. 36(8): 3789-94
1329. Taguchi, K. and Yamamoto, M. 2017. The KEAP1-Nrf2 system in cancer. Front Oncol. 7:85, doi: 10.3389/fonc.2017.00085, 11 pages
1330. Taipale, J., Chen, J. K., Cooper, M. K., Wang, B., Mann, R. K., Milenkovic, L., Scott, M. P. and Beachy, P. A. 2000. Effects of oncogenic mutations in smoothened and patched can be reversed by cylopamine. Nature. 406(6799): 1005-9
1331. Taira, J., Sugishima, M., Kida, Y., Oda, E., Noguchi, M. and Higashimoto, Y. 2011. Caveolin-1 is a competitive inhibitor of heme oxygenase-1(HO-1) with heme: identification of a minimum sequence in caveolin-1 for binding to HO-1. Biochemistry. 50(32): 6824-31
1332. Takada, Y., Andreeff, M. and Aggarwal, B. B. 2005. Indole-3-carbinol suppresses NF-kB and IkBα kinase activation, causing inhibition of expression of NF-kB-regulated antiapoptotic and metastatic gene products and enhancement of apoptosis in myeloid and leukemia cells. Blood. 106(2): 641-649
1333. Takahashi, R., Hirata, Y., Sakitani, K., Nakata, W., Kinoshita, H., Hayakawa, H., Sakamoto, K., Hikiba, Y., Ijichi, H., Moses, H. L., Maeda, S. and Koike, K. 2013. Therapeutic effect of c-Jun N-terminal kinase inhibition on pancreatic cancer. Cancer Sci. 104(3): 337-44
1334. Takeshima, M., Ono, M., Higuchi, T., Chen, C., Hara, T. and Nakano, S. 2014. Anti-proliferative and apoptosis-inducing

activity of lycopene against three subtypes of human breast cancer cell lines. Cancer Sci. 105(3): 252-257

1335. Tamimi, M. R., Hankinson, E. S., Campos, H., Spiegelman, D., Zhang, S., Colditz, A. G., Willett, C. W. and Hunter, J. D. 2005. Plasma carotenoids, retinol and tocopherols and risk of breast cancer. American Journal of Epidemiology. 161(2): 153-160

1336. Tan, H. W. S., Sim, A. Y. L. and Long, Y. C. 2017. Glutamine metabolism regulates autophagy-dependent mTORC1 reactivation during amino acid starvation. Nature Communications. 8: 338, doi: 10.1038/s41467-017-00369-y, 10 pages

1337. Tang, A., Cao, X., Tian, L., He, L and Liu, F. 2015. Apigenin inhibits the self-renewal capacity of human ovarian cancer SKOV3-derived sphere-forming cells. Molecular Medicine Reports. 11: 2221-2226, 2015, DOI: 10.3892/mmr.2014.2974

1338. Tang, F. Y., Shih, C. J., Cheng, L. H., Ho, H. J. and Chen, H. J. 2008. Lycopene inhibits growth of human colon cancer cells via suppression of the Akt signaling pathway. Mol Nutr Food Res. 52(6): 646-54

1339. Tang, Q., Su, Z., Han, Z. and Ma, X. 2012. LC-MS method for detecting prostratin in plant extracts and identification of a high-yielding population of *Euphorbia fischeriana*. Phytochemistry Letters. 5(1): 214-218, doi: 10.1016/j.phytol.2011.12.011

1340. Tang, X., Pan, Y. and Zhao, Y. 2013. Vitamin D inhibits the expression of interleukin-8 in human periodontal ligament cells stimulated with *Porphyromonas gingivalis*. Archives of Oral Biology. 58(4): 397-407

1341. Taniguchi, K., Petersson, M., Höglund, P., Kiessling, R., Klein, G. and Kärre, K. 1987. Interferon gamma induces lung colonization by intravenously inoculated B16 melanoma cells in parallel with enhanced expression of class I major histocompatibility complex antigens. Proc Natl Acad Sci USA. 84(10): 3405-9

1342. Tao, W., Liang, X., Liu, Y., Wang, C. and Pang, D. 2015. Decrease of Let-7f in low-dose metronomic paclitaxel chemotherapy contributed to upregulation of thrombospondin-1 in breast cancer. Int J Biol Sci. 11(1): 48-58, doi: 10.7150/ijbs.996

1343. Tarapore, R., Siddiqui, I. A., Adhami, V. M., Spiegelman, V. S. and Mukhtar, H. 2013. The dietary terpene lupeol targets colorectal cancer cells with constitutively active Wnt/β-catenin signaling. Mol Nutr Food Res. 57(11): 10.1002/mnfr.201300155, doi: 10.1002/mnfr.201300155, 16 pages
1344. Tarumoto, T., Nagai, T., Ohmine, K., Miyoshi, T., Nakamura, M., Kondo, T., Mitsugi, K., Nakano, S., Muroi, K., Komatsu, N. and Ozawa, K. 2004. Ascorbic acid restores sensitivity to imatinib via suppression of nrf2-dependent gene expression in the imatinib-resistant cell line. Exp Hematol. 32(4): 375-81
1345. Tashiro, E., Yokouchi, Y., Yamamoto, K. and Imoto, M. 2009. Abstract B150: Toyocamycin inhibits ER stress-induced XBP1 mRNA splicing through IRE1α activation. Molecular Cancer Therapeutics. 8(12 Suppl): B150, doi: 10.1158/1135-7163. TARG-09-B150
1346. Tate, C. M., Blosser, W., Wyss, L., Evans, G., Xue, Q., Pan, Y. and Stancato, L. 2013. LY2228820 dimesylate, a selective inhibitor of p38 mitogen-activated protein kinase, reduces angiogenic endothelial cord formation in vitro and in vivo. J Biol Chem. 288(9): 6743-53
1347. Tategu, M., Arauchi, T., Tanaka, R., Nakagawa, H. and Yoshida. 2008. Puma is a novel target of soy isoflavone genistein but is dispensable for genistein-induced cell fate determination. Mol Nutr Food Res. 52:439-446, doi: 10.1002/mnfr.200700218
1348. Tatsuta, K., Misawa, H. and Chikauchi, K. 2001. Biometric total synthesis of quinolactacin B, TNF production inhibitor, and its analogs. J Antibiot (Tokyo). 54 (1): 109-12 https: // doi.org / 10.7164 / antibiotics. 54. 109
1349. Tavani, A., Bertuccio, P., Bosetti, C., Talamini, R., Negri, E., Franceschi, S., Montella, M. and LaVecchia, C. 2005. Dietary intake of calcium, vitamin D, phosphorus and the risk of prostate cancer. European Urology. 48(1):27-33 DOI: https:// doi.org/10.1016/j.eururo.2005.03.023
1350. Taves, S., Berta, T., Liu, D. L., Gan, S., Chen, G., Kim, Y. H., Van de Ven, T., Laufer, S. and Ji, R. R. 2016. Spinal inhibition of p38 MAP kinase reduces inflammatory and neuropathic pain

in male but not female mice: Sex-dependent microglial signaling in the spinal cord. Brain Behav Immun. 55:70-81, doi: 10.1016/j. bbi, 2015.10.006

1351. Tayarani-Najarani, Z., Asili, J., Parsaee, H., Mousavi, S. H., Mashhadian, N. V., Mirzaee, A. and Emami, S. A. 2012. Wogonin and neobaicalein from Scutellaria litwinowii roots are apoptotic for HeLa cells. Brazilian Journal of Pharmacognosy. 22(2): 268-276

1352. Taye, N., Alam, A., Ghorai, S., Chatterji, D. G., Parulekar, A., Mogare, D., Singh, S., Sengupta, P., Chatterjee, S., Bhat, M. K., Santra, M. K., Salunkhe, P. B., Finston, S. K. and Chattopadhyay, S. 2018. SMAR1 inhibits Wnt/β-catenin signaling and prevents colorectal cancer progression. Oncotarget. 9(30): 21322-21336

1353. Tayyem, R. F., Heath, D. D., Al-Delaimy, W. K. and Rock, C. L. 2006. Curcumin content of turmeric and curry powders. Nutr Cancer. 55(2): 126-31

1354. Teachey, D. T., Obzut, D. A., Cooperman, J., Fang, J., Carroll, M., Choi, J. K., Houghton, P. J., Brown, V. I. and Grupp, S. A. 2006. The mTOR inhibitor CCI-779 induces apoptosis and inhibits growth in preclinical models of primary adult human ALL. Blood. 107(3): 1149-55

1355. Tejasari, D. 2007. Evaluation of ginger (*Zingiber officinale Roscoe*) bioactive compounds in increasing the ratio of T-cell surface molecules of CD3+CD4+:CD3+CD8+in vitro. Malays J Nutr. 13(2): 161-70

1356. Teodorczyk, M. and Schmidt, M. H. H. 2015. Notching on cancer's door: Notch signaling brain tumors. Frontiers in Oncology. 4: 341, doi: 10.3389/fonc.2014.00341, 14 pages

1357. Teranishi, F., Takahashi, N., Gao, N., Akamo, Y., Takeyama, H., Manabe, T. and Okamoto, T. 2009. Phosphoinositide 3-kinase inhibitor (wortmannin) inhibits pancreatic cancer cell motility and migration induced by hyaluronan in vitro and peritoneal metastasis in vivo. Cancer Sci. 100(4): 770-7

1358. Teupser, D., Thiery, J. and Seidel, D. 1999. α-tocopherol down-regulates scavenger receptor activity in macrophages. Atherosclerosis. 144(1): 109-115, https:// doi.org/10.1016/S0021-9150(99)80424-9

1359. Thaxton, J. E., Wallace, C., Riesenberg, B., Zhang, Y., Paulos, C. M., Baeson, C. C., Liu, B. and Li, Z. 2017. Modulation of endoplasmic reticulum stress controls CD4+T-cell activation and antitumor function. Cancer Immunol Res. 5(8): 666-675
1360. The Alpha-Tocopherol Beta Carotene Cancer Prevention Study Group. 1994. The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. The New England Journal of Medicine. 330: 1029-1035, doi: 10.1056/NEJM199404143301501.
1361. Theodoratou, E., Farrington, S. M., Tenesa, A., McNeill, G., Cetnarskyj, R., Barnetson, R. A., Porteous, M. E., Dunlop, M. G. and Campbell, H. 2008. Dietary vitamin B_6 intake and the risk of colorectal cancer. Cancer Epidemiology Biomarkers and Prevention. 17(1):171-182, doi: 10.1158/1055-9965.EPI-07-0621.
1362. Theytaz, F., de Giorgi, S., Hodson, L., Stefanoni, N., Rey, V., Schneiter, P., Giusti, V. and Tappy, L. 2014. Metabolic fate of fructose ingested with and without glucose in a mixed meal. Nutrients. 6(7): 2632-49
1363. Thiel, G. and Rössler, O. G. 2014. Resveratrol stimulates AP-1-regulated gene transcription. Mol Nutr Food Res. 58(7): 1402-13
1364. Thiel, G., Ulrich, M., Mukaida, N. and Rössler, O. G. 2018. Resveratrol stimulation induces interleukin-8 gene transcription via NF-kB. Pharmacological Research. 134: 238-245, https://doi.org/10.1016/j.phrs.2018.07.003
1365. Thomas, D., Cherest, H. and Surdin-Kerjan, Y. 1991. Identification of the structural gene for glucose-6-phosphate dehydrogenase in yeast. Inactivation leads to a nutritional requirement for organic sulfur. The EMBO Journal. 10(3): 547-53
1366. Thornton, T. M., Pedraza-Alva, G., Deng, B., Wood, C. D., Aronshtam, A., Clements, J., Sabio, G., Davis, R. J., Matthews, D. E., Double, B. and Rincon, M. 2008. Phosphorylation by p38 MAPK as an alternative pathway for GSK3beta inactivation. Science. 320 (5876): 667-70
1367. Tiffon, C. E., Adams, J. E., van der Fits, L., Townsend, P. A., Ganesan, A., Hodges, E., Vermeer, M. H. and Packham, G. 2011.

The histone deactylase inhibitors vorinostat and romidepsin downmodulate IL-10 expression in cutaneous T-cell lymphoma cells. British Journal of Pharmacology. 162(7): 1590-1602

1368. Tin, A. S., Park, A. H., Sundar, S. N. and Firestone, G. L. 2014. Essential role of the cancer stem/progenitor cell marker nucleostemin for indole-3-carbinol anti-proliferative responsiveness in human breast cancer cells. BMC Biology. 12:72, http://www.biomedcentral.com/1741-7007/12/72, 22 pages

1369. Toiyama, Y., Inoue, Y., Hiro, J., Ojima, E., Watanabe, H., Narita, Y., Okigami, M., Hosono, A., Miki, C. and Kusunoki, M. 2009. Paclitaxel inhibits radiation induced VEGF secretion and enhances radiosensitizing effects in human colon cancer cell HT29. Cancer Therapy. 123-132 (Electronically published only).

1370. Tongers, J., Fiedler, B., Konig, D., Kempf, T., Klein, G., Heineke, J., Kraft, T., Gambaryan, S., Lohmann, S. M., Drexler, H. and Wollert, K. C. 2004. Heme oxygenase-1 inhibition of MAP kinases, calcineurin/NFAT signaling, and hypertrophy in cardiac myocytes. Cardiovascular Research. 63(3): 545-552

1371. Topol, L., Chen, W., Song, H., Day, T. F. and Yang, Y. 2009. Sox9 inhibits Wnt signaling by promoting β-catenin phosphorylation in the nucleus. J Biol Chem. 284(5): 3323-3333

1372. Toppo, S., Flohe, L., Ursini, F., Vanin, S. and Maiorino, M. 2009. Catalytic mechanisms and specificities of glutathione peroxidases of a basic scheme. Biochim Biophys Acta. 1790(11):1486-1500

1373. Torkin, R., Lavoie, J., Kaplan, R. D. and Yeger, H. 2005. Induction of caspase-dependent p53-mediated apoptosis by apigenin in human neuroblastoma. Mol Cancer Ther. 4(1): 1-11, PMID:15657348

1374. Torrisani, J., Bournet, B., du Rieu, M. C., Bouisson, M., Sougue, A., Escourrou, J., Buscail, L. and Cardelier, P. 2009. Let-7 microRNA transfer in pancreatic cancer-derived cells inhibits in vitro cell proliferation but fails to alter tumor progression. Hum Gene Ther. 20(8): 831-44

1375. Tortorella, S. M., Royce, G. S., Licciardi, P. V. and Karagiannis, C. T. 2015. Dietary sulforaphane in cancer chemoprevention: The

role of epigenetic regulation and HDAC inhibition. Antioxidants & Redox Signaling. 22(16): 1382-1424

1376. Totusek, J., Triska, J., Lefnerova, D., Strohalm, J., Vrchotova, N., Zendulka, O., Pruchova, J., Chaloupkova, J., Novotna, P. and Houska, M. 2011. Contents of sulforaphane and total isothiocyanates, antimutagenic activity and inhibition of clastogenicity in pulp juices from cruciferous plants. Czech J Food Sci. 29(5): 548-556

1377. Touvier, M., Kesse, E., Clavel-Chapelon, F., Boutron-Ruault, M. 2005. Dual association of beta-carotene with risk of tobacco-related cancers in a cohort of French women. J Natl Cancer Inst. 97(18): 1338-44

1378. Traka, M., Gasper, A. V., Melchini, A., Bacon, J. R., Needs, P. W., Frost, V., Chantry, A., Jones, A. M., Ortori, C. A., Barrett, D. A., Ball, R. Y., Mills, R. D. and Mithen, R. F. 2008. Broccoli consumption interacts with GSTM1 to perturb oncogenic signaling pathways in the prostate. Plos One. 3(7): e2568, doi: 10.1371/journal.pone.0002568, 14 pages

1379. Tremblay, M. R., Nesler, M., Weatherhead, R. and Castro, A. C. 2009. Recent patents for Hedgehog pathway inhibitors for the treatment of malignancy. Expert Opin Ther Pat. 19(8): 1039-56

1380. Trifilieff, A., Keller, T. H., Press, N. J., Howe, T., Gedeck, P., Beer, D. and Walker, C. 2005. CGH2466, a combined adenosine receptor antagonist, p38 mitogen-activated protein kinase and phosphodiesterase type 4 inhibitor with potent in vitro and in vivo anti-inflammatory activities. Br J Pharmacol. 144(7): 1002-10

1381. Troyer, D. and Fernandes, G. 1996. Nutrition and apoptosis. Nutrition Research. 16(11-12): 1959–1987.

1382. Tsai, C., Chen, W., Hsieh, H., Chi, P., Hsiao, L. and Yang, C. 2014. TNF-α induces matrix metalloproteinase-9-dependent soluble intercellular adhesion molecule-1 release via TRAF2-mediated MAPKs and NF-kB activation is osteoblast-like MC3T3-E1 cells. Journal of Biomedical Science. 21:12, https:// doi.org/10.1186/1423-0127-21-12, 19 pages

1383. Tsui, K., Feng, T., Hsieh, W., Chang, P. and Juang, H. 2008. Expression of interleukin-6 is downregulated by

17-(allylamino)-176-demethoxygeldanamycin in human prostatic carcinoma cells. Acta Pharmacologica Sinica. 29(11): 1334-1341

1384. Tsuruga, E., Irie, K. and Yajima, T. 2007. Fibrillin-2 degradation by matrix metalloproteinase-2 in periodontium. J Dent Res. 86(4): 352-6

1385. Tunçel, G., Nout, R. J. M. and Brimer, L. 1995. The effects of grinding, soaking and cooking on the degradation of amygdalin of bitter apricot seeds. Food Chemistry. 53(4): 447-451

1386. Tyagi, S., Sharma, S. and Budhiraja, R. D. 2012. Effect of phosphatidylinositol 3-kinase-Y inhibitor CAY10505 in hypertension, and its associated vascular endothelium dysfunction in rats. Can J Physiol Pharmacol. 90(7): 881-5

1387. U.S. Department of Agriculture, Agricultural Research Service. 2011. USDA National Nutrient database for standard reference, release 24. Nutrient Data Laboratory home page, http://www.ars.usda.gov/ba/bhnrc/ndl

1388. U.S.Department of Agriculture, Agricultural Research Service . 2014. http:_//_ods.od.nih.gov_/_factsheets_/_vitamin D-HealthProfessional.

1389. U.S.Department of Agriculture, Agricultural Research Service. 2012. USDA National Nutrient Database for Standard Reference, Release 25

1390. U.S.Department of Agriculture, Agricultural Research Service. USDA. 2016. National Nutrient Database for Standard Reference. Release 28 slightly revised. May, 2016.

1391. Uehara, N., Yoshizawa, K. and Tsubura, A. 2012. Vorinostat enhances protein stability of p27 and p21 through negative regulation of Skp2 and Cks1 in human breast cancer cells. Oncol Rep. 28: 105-10, doi: 10.3892/or.2012.1758

1392. Uehara, Y., Mochizuki, Matsuno, K., Haino, T. and Asai, A. 2009. Novel high-throughput screening system for identifying STAT3-SH2 antagonists. Biochem Biophys Res Commun. 380(3): 627-31

1393. Uhlmann, S., Friedrichs, U., Eichler, W., Hoffmann, S. and Wiedemann, P. 2001. Direct measurement of VEGF-induced

nitric oxide production by choroidal endothelial cells. Microvasc Res. 62(2): 179-89

1394. Ullah, M. F., Ahmad, A., Zubair, H., Khan, H. Y., Wang, Z., Sarkar, F. H. and Hadi, S. M. 2011. Soy isoflavone genistein induces cell death in breast cancer cells through mobilization of endogenous copper ions and generation of reactive oxygen species. Mol Nutr Food Res. 55: 553-559, doi: 10.1002/mnfr.201000329

1395. Underwood, D. C., Osborn, R. R., Kotzer, C. J., Adams, J. L., Lee, J. C., Webb, E. F., Carpenter, D. C., Bochnowicz, S., Thomas, H. C., Hay, D. W. and Griswold, D. E. 2000. SB239063, a potent p38 MAPkinase inhibitor, reduces inflammatory cytokine production, airways eosinophil infiltration, and persistence. J Pharmacol Exp Ther. 293(1): 281-8, PMID:10734180

1396. Urs, S., Turner, B., Tang, Y., Rostama, B., Small, D. and Liaw, L. 2012. Effect of soluble Jagged1-mediated inhibition of Notch signaling on proliferation and differentiation of an adipocyte progenitor cell model. Adipocyte. 1(1): 46-57, doi: 10.4161/adip.19186

1397. USDA. 2015. National Nutrient Database for Standard Reference Release 28, October 19, 2015.

1398. USDA. 2016. United States Department of Agriculture. Agricultural Research Service: Nutritional Nutrient Database for Standard Reference Release 28, Software v.2.3.4.2, The National Agricultural Library. ndb.nal.usda.gov/ndb/nutrients/arginine

1399. USDA. Technical Evaluation Report. 2012. β-carotene. Handling / Processing. https:// www.ams.usda.gov. 24 pages

1400. Vadlapatla, R. K., Vadlapudi, A. D., Pal, D., Mukherji, M. and Mitra, A. K. 2014. Ritonavir inhibits HIF-1α-mediated VEGF expression in retinal pigment epithelial cells in vitro. Eye. 28(1): 93-101, doi: 10.1038/eye.2013.240

1401. Van den Donk, M., Visker, M. H. P. W., Harryvan, J. L., Kok, F. J. And Kampman, E. 2007. Dietary intake of B-vitamins, polymorphisms in thymidylate synthase and serine hydroxymethyltransferase 1 and colorectal adenoma risk: A

dutch case-control study. Cancer Letters. 250(1): 146-153, doi: 10.1016/j.canlet.2006.10.002

1402. Van der Holt, B., Löwenberg, B., Burnett, A. K., Wolfgang, U., Shepherd, J., Piccaluga, P. P., Ossenkoppele, G. J., Verhoef, G. E. G., Ferrant, A., Crump, M., Selleslag, D., Theobald, M., Fey, M. F., Vellenga, E., Dugan, M. and Sonneveld, P on behalf of the Dutch-Belgian Hemato-Oncology Cooperative Group (HOVON) and the United Kingdom Medical Research Council (MRC). 2005. The value of the MDR-1 reversal agent PSC-833 in addition to daunorubicin and cytarabine in the treatment of elderly by patients with previously untreated acute myeloid leukemia (AML), in relation to MDR1 status at diagnolsis. Blood. 106: 2646-2654, doi: https://doi.org/10.1182/blood-2005-04-1395

1403. Van Geldermalsen, M., Wang, Q., Nagarajah, R., Marshall, A. D., Thoeng, A., Gao, D., Ritchie, W., Feng, Y., Bailey, C. G., Deng, N., Harvey, K., Beith, J. M., Selinger, C. I., O'Toole, S. A., Rasko, J. E. and Holst, J. 2016. ASCT2/SLC1A5 controls glutamine uptake and tumour growth in triple-negative basal-like breast cancer. Oncogene. 35(24): 3201-8

1404. Van Tine, B. A., Crowder, R. J. and Ellis, M. J. 2011. ER and PI3K independently modulate endocrine resistance in ER-positive breast cancer. Cancer Discov. 1(4): 287-8

1405. Varsha, K., Sharma, A., Kaur, A., Madan, J., Pandey, R. S., Jain, U. K. and Chandra, R. 2017. Chapter 28-Natural plant-derived anticancer drugs nanotherapeutics: a review on preclinical to clinical success. Nanostructures for Cancer Therapy. Papers: 775-809, https:// doi.org/10.1016/B978-0-323-46144-3.00028-3

1406. Vasamsetti, S. B., Karnewar, S., Kanugula, A. K., Thatipalli, A. R., Kumar, J. M. and Kotamraju, S. 2015. Metformin inhibits monocyte-to-macrophage differentiation via AMPK-mediated inhibition of STAT3 activation: potential role in atherosclerosis. Diabetes. 64(6): 2028-41

1407. Verbeek, R., Plomp, A. C., van Tol, A. F. and van Noort, J. M. 2004. The flavones luteolin and apigenin inhibit in vitro antigen-specific proliferation and interferon-gamma production

by murine and human autoimmune T cells. Biochemical Pharmacology. 68: 621-629, doi: 10.1016/j.bcp.2004.05.012

1408. Verhoeven, D. T. H., Assen, N., Goldbohm, R. A., Dorant, E., van't Veer, P., Sturmans, F., Hermus, R. J. J. and van den Brandt, P. A. 1997. Vitamins C and E, retinol, beta-carotene and dietary fibre in relation to breast cancer risk: a prospective cohort study. British Jornal of Cancer. 75(1): 149-155, PMID: 9000614

1409. Verkaar, F., van der Doelen, A. A., Smiths, J. F., Blankesteijn, W. M. and Zaman, G. J. 2011. Inhibition of Wnt/β-catenin signaling by p38 MAPkinase inhibitors is explained by cross-reactivity with casein kinase 1δ/ε. Chem Biol. 18(4): 485-94

1410. Verway, M., Bouttier, M., Wang, T., Carrier, M., Calderon, M., An, B., Deremy, E., McIntosh, F., Divangahi, M., Behr, M. A. and White, J. H. 2013. Vitamin D induces interleukin-1B expression: macrophage epithelial signaling controls *M. tuberculosis* infection. PlosPathog. 9(6):e1003407, doi: 10.1371/journal.ppat.1003407, 14 pages

1411. Viswanathan, S. R., Powers, J. T., Einhorn, W., Hoshida, Y., Ng, T. L., Toffanin, S., O'Sullivan, M., Lu, J., Phillips, L. A., Lockhart, V. L., Shah, S. P., Tanwar, P. S., Mermel, C. H., Beroukhim, R., Azam, M., Teixeira, J., Meyerson, M., Hughes, T. P., Llovet, J. M., Radich, J., Mullighan, C. G., Golub, T. R., Sorensen, P. H. and Daley, G. Q. 2009. Lin28 promotes transformation and is associated with advanced human malignancies. Nat Genet. 41(7): 843-8

1412. Vitrac, X., Bornet, A., Vanderlinde, R., Valls, J., Richard, T., Delaunay, J., Merillon, J. and Teissedre, P. 2005. Determination of stilbenes (δ-viniferin, trans-astringin, trans-piceid, cis-and trans-resveratrol, e-viniferin) in Brazilian wines. J Agric Food Chem. 53(14): 5664-5669

1413. Voigt, C., May, P., Gottschlich, A., Markota, A., Wenk, D., Gerlach, I., Voigt, S., Stathopoulos, G. T., Kam, A., Heise, C., Rataj, F., Janssen, K. P., Königshoff, M., Winter, H., Himsl, I., Thasler, W. E., Schnurr, M., Rothenfußer, S., Endres, S. and Kobold, S. 2017. Cancer cells induce interleukin-22 production from memory CD4+ T cells via interleukin-1 to promote tumor growth. Proc Natl Acad Sci USA. 114(49): 12994-11999

1414. Voigt, J. M. 2006. Inhibition of AP-1 activity in MCF-7 cells by vitamin D3 and VDUP-1. Cancer Res. 66(Supl 8): 401-409

1415. Von Hoff, D. D., LoRusso, P. M., Rudin, C. M., Reddy, J. C., Yauch, R. L., Tibes, R., Weiss, G. J., Borad, M. J., Hann, C. L., Brahmer, J. R., Mackey, H. M., Lum, B. L., Darbonne, W. C., Marsters, J. C., de Sauvage, F. J. and Low, J. A. 2009. Inhibition of the hedgehog pathway in advanced basal-cell carcinoma. N Engl J Med. 361(12): 1164-72

1416. Voorrips, L. E., Goldbohm, R. A., Brants, H. A. M., van Poppel, G. A. F. C., Sturmans, F., Hermus, R. J. J. and van den Brandt, P. A. 2000. A prospective cohort study on antioxidant and folate intake and male lung cancer risk. Cancer Epidemiol Biomarkers Prev. 9(4):357-365

1417. Voronkov, A. and Krauss, S. 2012. Wnt/beta-catenin signaling and small molecule inhibitors. Curr Pharm Des. 19(4): 634-664

1418. Vrieling, A., Hein, R., Abbas, S., Schneeweiss, A., Flesch-Janys, D. and Chang-Claude, J. 2011. Serum 25-hydroxyvitamin D and postmenopausal breast cancer survival: a prospective patient cohort study. Breast Cancer Research. 13(4):R74-R83

1419. Wagner, F. E. and Nebreda, R. A. 2009. Signal intergration by JNK and p38 MAPK pathways in cancer development. Nature Reviews Cancer. 9: 537-549, doi: 10.1038/nrc2694

1420. Wagner, K. R., Hua, Y., de Courten-Myers, G. M., Broderick, J. P., Nishimura, R. N., Lu, S. Y. and Dwyer, B. E. 2000. Tin-mesoporphyrin, a potent heme oxygenase inhibitor for treatment of intracerebral hemorrhage: in vivo and in vitro studies. Cell Mol Biol. 46(3): 597-608

1421. Waldner, M. J., Foersch, S. and Neurath, M. F. 2012. Interleukin-6-a key regulator of colorectal cancer development. Int J Biol Sci. 8(9): 1248-1253

1422. Walker, T., Mitchell, C., Park, M. A., Yacoub, A., Rahmani, M., Haussinger, D., Reinehr, R., Voelkel-Johnson, C., Fisher, P. B., Grant, S. and Dent, P. 2010. 17AAG and MEK1/2 inhibitors kill GI tumor cells via Ca^{2+} dependent suppression of GRP78/BİP and induction of ceramide and ROS. Mol Cancer Ther. 9(5): 1378-1395

1423. Wallin, J. J., Edgar, A. K., Guan, J., Berry, M., Prior, W. W., Lee, L., Lesnick, D. J., Lewis, C., Nonomiya, J., Pang, J., Salphati, L., Olivero, G. A., Sutherlin, P. D., O'Brien, C., Spoerke, M. J., Patel, S., Lensun, L., Kassees, R., Ross, L., Lackner, R. M., Sampath, D., Belvin, M. and Friedman, S. L. 2011. GDC-0980 is a novel class 1 PI3K/mTOR kinase inhibitor with robust activity in cancer models driven by the PI3K pathway. Mol Cancer Ther. 10(12): 2426-36

1424. Wallstab, A., Koester, M., Böhme, M. and Keppler, D. 1999. Selective inhibition of MDR1 P-glycoprotein-mediated transport by the acridone carboxamide derivative GG918. Br J Cancer. 79(7-8): 1053-1060

1425. Wan, L. L., Xia, J., Ye, D., Liu, J., Chen, J. and Wang, G. 2009. Effects of quercetin on gene and protein expression of Nox and Nos after myocardial ischemia and reperfusion in rabbit. Cardiovascular Therapeutics. 27: 28-33, doi: 10.1111/j.1755-5922.2009.00071.x

1426. Wang, C., Wen, J., Zhou, Y., Li, L., Cui, X., Wang, J., Pan, L., Ye, Z., Li, P. and Wu, L. 2015. Apelin induces vascular smooth muscle cells migration via a PI3K/Akt/Foxo3a/MMP-2 pathway. Int J Biochem Cell Biol. 69:173-82, doi:10.1016/j. biocel.2015.10.015

1427. Wang, D. and DuBois, N. R. 2010. The role of COX-2 in intestinal inflammation and colorectal cancer. Oncogene. 29(6): 781-788

1428. Wang, D., Kong, X., Li, Y., Qian, W., Ma, J., Wang, D., Yu, D. and Zhong, C. 2017. Curcumin inhibits bladder cancer stem cells by suppressing sonic Hedgehog pathway. Biochemical and Biophysical Research Communications. 493: 521-527, http:// dx.doi.org/10.1016/j.bbrc.2017.08.158

1429. Wang, F., Chen, L., Zhu, S., Wang, S., Chen, C., Zhang, W., Wang, X., Zhang, J. and Wang, M. 2018. Sulforaphane induces apoptosis of acute human leukemia cells through modulation of Bax, Bcl-2 and caspase 3. International Journal of Pharmacology. 14:369-376, doi:10.3923/ijp.2018.369.376

1430. Wang, F., Zhang, D., Zhang, Q., Chen, Y., Zheng, D., Hao, L., Duan, C., Jia, L., Liu, G. and Liu, Y. 2011. Synergistic effect

of folate-mediated targeting and verapamil-mediated P-gp inhibition with paclitaxel –polymer micelles to overcome multi-drug resistance. Biomaterials. 32(35): 9444-56

1431. Wang, G., Jin, J., Zeng, J., Shi, R., Dai, Y., Wu, J., Li, Y., Wang, T.and Ma, Y. 2017. Involvement of P-glycoprotein and multidrug and toxin extrusion protein 1 in hepatic and renal berberine efflux in mice. The Royal Society of Chemistry. 7: 34801-34809, doi: 10.1039/c7ra01643c

1432. Wang, H., Jia, X., Sui, C., Zhao, Y., Mei, Y., Zheng, Y. and Zhang, Z. 2014. Effects of thapsigargin on the proliferation and survival of human rheumatoid arthritis synovial cells. The Scientific Worl Journal. Article ID 605416, Vol. 2014, doi: http: // dx.doi.org / 10.1155 / 2014 / 605416, 7 pages

1433. Wang, H., Liu, K., Geng, M., Gao, P., Wu, X., Hai, Y., Li, Y., Li, Y., Luo, L., Hayes, D. J., Wang, J. X. and Tang, X. 2013. RxRα inhibits the Nrf2-Are signaling pathway through a direct interaction with the Neh7 domain of nrf2. Cancer Res. 73(10): 3097-108

1434. Wang, J., Li, Y. and Qi, Y. 2017. Effect of glutamine-enriched nutritional support on intestinal mucosal barrier function, MMP-2, MMP-9 and immune function in patients with advanced gastric cancer during perioperative chemotherapy. Oncol Lett. 14(3): 3603-3610

1435. Wang, J., Liao, Y., Fan, J., Ye, T., Sun, X. and Dong, S. 2012. Apigenin inhibits the expression of IL-6, IL-8, and ICAM-1 in DEPH-stimulated human umbilical vein endothelial cells and in vitro. Inflammation. 35(4): 1466-1476

1436. Wang, J., Yin, Y., Hua, H., Li, M., Luo, T., Xu, L., Wang, R., Liu, D., Zhang, Y. and Jiang, Y. 2009. Blockade of GRP78 sensitizes breast cancer cells to microtubules-interfering agents that induce the unfolded protein response. J Cell Mol Med. 13(9b): 3888-3897; doi: 10.1111/j.1582-4934.2009.00873.x

1437. Wang, L., Lee, I., Zhang, S. M., Blumberg, J. B., Buring, J. E. and Sesso, H. D. 2009. Dietary intake of selected flavonols, flavones and flavonoid-rich foods and risk of cancer in middle-aged and older women. Am J Clin Nutr. 89(3): 905-12

1438. Wang, L., Li, J., Guo, L., Li, P., Zhao, Z., Zhou, H. and Di, L. 2008. Molecular link between glucose and glutamine consumption in cancer cells mediated by CtBP and SIRT4. Oncogenesis. 7:26, doi: 10.1038/s41389-018-0036-8, 10 pages
1439. Wang, L., Tai, C., Chien, C., Chiang, F. and Chen, J. Y. 2015. Vitamin D decreases the secretion of matrix metalloproteinase-2 and matrix metalloproteinase-9 in fibroblasts derived from Taiwanese patients with chronic rhinosinusitis with nasal polyposis. The Kaohsiung Journal of Medical Sciences. 31(5): 235-240
1440. Wang, L., Walia, B., Evans, J., Gevirtz, A. T., Merlin, D. and Sitaraman, S. V. 2003. IL-6 induces NF-kappaB activation in the intestinal epithelia. J Immunol. 171(6): 3194-201
1441. Wang, M., Lin, S., Hou, Y. and Chen, Y. 2016. Suppression of lipid accumulation by indol-3-carbinol is associated with increased expression of the aryl hydrocarbon receptor and CYP1B1 proteins in adipocytes and with decreased adipocyte-stimulated endothelial tube formation. Int J Mol Sci. 17(8): 1256, doi:10.3390/ijms17081256, 11 pages
1442. Wang, M., Simon, J. E., Aviles, I. F., He, K., Zheng, Q. Y. and Tadmor, Y. 2003. Analysis of antioxidative phenolic compounds in artichoke (Cynara scolymus L.). J Agric Food Chem. 51(3): 601-8
1443. Wang, R., Jiao, H., Zhao, J., Wang, X. and Lin, H. 2018. L-arginine enhances protein synthesis by phosphorylating mTOR (Thr 2446) in a nitric oxide-dependent manner in C2C12 cells. Oxid Med Cell Longev. 2018: 7569127, doi: 10.1155/2018/7569127, 13 pages
1444. Wang, T., Lu, S., Xia, Q., Fang, Z. and Johnson, S. 2015. Separation and purification of amygdalin from thinned boyberry kernels by macroporous adsorption resins. Journal of Chromatography B. 975: 52-58, http://dx.doi.org/1016/j.jchromb.2014.10.038
1445. Wang, W., Liu, H., Wang, S., Hao, X. and Li, L. 2011. A diterpenoid derivative 15-oxospiramilactone inhibits Wnt/β-catenin signaling and colon cancer cell tumorigonesis. Cell Res. 21(5): 730-740

1446. Wang, W., Xu, D., Wang, B., Yan, S., Wang, X., Yin, Y., Wang, X., Sun, B. and Sun, X. 2015. Increased risk of cancer in relation to gout: A review of three prospective cohort studies with 50.358 subjects. Mediators of Inflammation. Volume 2015. Article ID 680853, 6 pages, http://dx.doi.org/10.1155/680853

1447. Wang, X. J., Hayes, D. J., Henderson, C. J. and Wolf, C. R. 2007. Identification of retinoic acid as an inhibitor of transcription factor Nrf2 through activation of retinoic acid receptor alpha. Proc Natl Acad Sci USA. 104(49): 19589-19594

1448. Wang, X. M., Wu, T. X., Lee, Y. S. and Dionne, R. A. 2006. Rofecoxib regulates the expression of genes related to the matrix metalloproteinase pathway in humans: implication for the adverse effects of cyclooxygenase-2inhibitors. Clin Pharmacol Ther. 79(4): 303-15

1449. Wang, X., Chao, K., Chen, Z., Arbiser, J. and Shin, D. 2007. Honokiol reduces drug resistance by inhibition of P-glycoprotein drug resistance by inhibition of P-glycoprotein expression in multidrug resistant (MDR) squamous cell carcinoma of the head and neck (SCCHN). Cellular and Molecular Biology. 67(9): Suppl, AACR Annula Meeting-Apr 14-18, 2007, Los Angeles, CA.

1450. Wang, X., Sun, Z., Villeneuve, N. F., Zhang, S., Zhao, F., Li, Y., Chen, W., Yi, X., Zheng, W., Wondrak, T. G., Wong, K. P. and Zhang, D. D. 2008. Nrf2 enhances resistance of cancer cells to chemotherapeutic drugs, the dark side of Nrf2. Carcinogenesis. 29(6): 1235-1243

1451. Wang, X., Wang, D. and Zhao, Y. 2015. Effect and mechanism of resveratrol on the apoptosis of lung adenocarcinoma cell line A549. Cell Biochemistry and Biophysics. 73(2):527-531

1452. Wang, X., Wang, Y. and Gao, W. 2015. Honokiol possesses potential anti-inflammatory effects on rheumatoid arthritis and GM-CSF can be a target for its treatment. Int J Clin Exp Pathol. 8(7): 7929-7936

1453. Wang, X., Witting, P. K., Salvatore, B. A. and Neuzil, J. 2005. Vitamin E analogs trigger apoptosis in HER2/erbB2-overexpressing breast cancer cells by signaling via the

mitochondrial pathway. Biochemical and Biophysical Research Communications. 326(2): 282-289

1454. Wang, X., Zhang, L., O'Neill, A., Bahamon, B., Alsop, D. C., Mier, J. W., Goldberg, S. N., Signoretti, S., Atkins, M. B., Wood, C. G. and Bhatt, R. S. 2013. Cox-2 inhibition enhances the activity of sunitinib in human renal cell carcinoma xenografts. Br J Cancer. 108(2): 319-26

1455. Wang, Y. and Marsden, A. P. 1995. Nitric Oxide Synthases: gene structure and regulation. Advances in Pharmacology. 34: 71-90, https://doi.org/10.1016/S1054-3589(08)61081-9

1456. Wang, Y., Jacobs, J. E., Newton, C. C. and McCullough, L. M. 2016. Lycopene, tomato products and prostate cancer-specific mortality among men diagnosed with nonmetastastatic prostate cancer in the cancer prevention study II nutrition cohort. International Journal of Cancer. 138(12): 2846-2855

1457. Wang, Y., Zhang, L., Fan, X., Wu, S. and Zhang, S. 2018. Poly-L-arginine induces apoptosis of NCI-H292 cells via ERK1/2 signaling pathway. Journal of Immunology Research. Volume 2018, Article ID 3651743, https://doi.org/10.1155/2018/3651743, 9 pages

1458. Wang, Y., Zhou, Y. and Graves, D. T. 2014. FOXO transcription factors: Their clinical significance and regulation. BioMed Research International. Vol. 2014, Article ID 925350, doi: Francis, R. E., Myatt, S. S., Krol, J., Hartman, J., Peck, B., McGovern, U. B., Wang, J., Guest, S. K., Filipovic, A., Gojis, O., Palmieri, C., Peston, D., Shousha, S., Yu, Q., Sicinski, P., Coombes, R. C. and Lam, E. W. 2009. FoxM1 is a downstream target and marker of HER2 overexpression in breast cancer. Int J Oncol. 35(1): 57-68, doi: 10.1155/2014/925350

1459. Wang, Z., Cheng, Y., Wang, N., Wang, D. M., Li, Y. W., Han, F., Shen, J. G., Yang de, P., Guan, X. Y. and Chen, J. P. 2012. Dioscin induces cancer cell apoptosis through elevated oxidative stress mediated by downregulation of peroxiredoxins. Cancer Biol Ther. 13(3): 138-47

1460. Waris, G. and Ahsan, H. 2006. Reactive oxygen species: role in the development of cancer and various chronic conditions. Journal of Carcinogenesis. 5(1): 14, doi: 10.1186/1477-3163-5-14

1461. Watabe, M., Machida, K. and Osada, H. 2000. MT-21 is a synthetic apoptosis inducer that directly induces cytochrome c release from mitochondria. Cancer Research. 60(18): 5214-5222
1462. Waziri, P. M., Abdullah, R., Rosli, R., Omar, A. R., Abdul, A. B., Kassim, N. K., Malami, I., Etti, I. C., Sani, J. M., Mohd Lila, M. A. and Abdullah, J. F. F. 2018. Clausenidin induces caspase 8-dependent apoptosis and suppresses production of VEGF in liver cancer cells. Asian Pac J Cancer Prev. 19(4): 917-922
1463. Weigin, L., Pelicano, H. and Huang, P. 2010. Cancer metabolism: Is glutamine sweeter than glucose?. Cancer Cell. 18(3): 199-200
1464. Weikl, F., Ghirardo, A., Schnitzler, J. and Pritsch, K. 2016. Sesquiterpene emissions from *Alternaria alternate* and *Fusarium oxysporum*: effects of age, nutrient availability, and co-cultivation. Scientific Reports. 6: 22152, doi: 10.1038/srep22152, 12 pages
1465. Weinberg, E. D. 1996. The role of iron in cancer. Eur J Cancer Prev. 5(1): 19-36, PMID: 8664805
1466. Weinstein, J.S., Wright, E. M., Pietinen, P., King, I., Tan, C., Taylor, R. P., Virtamo, J. and Albanes, D. 2005. Serum α-tocopherol in relation to prostate cancer risk in a prospective study. JNCI. 97(5): 396-399
1467. Weinstein, S. J., Albanes, D., Selhub, J., Graubard, B., Lim, U., Taylor, P. R., Virtamo, J. and Stolzenberg-Solomon, R. 2008. One-carbon metabolism biomarkers and risk of colon and rectal cancers. Cancer Epidemiol Biomarkers Prev. 17(11): 3233-3240
1468. Weiser, M. A., Cabanillas, M. E., Konopleva, M., Thomas, D. A., Pierce, S. A., Escalante, C. P., Kantarjian, H. M. and O'Brien, S. M. 2004. Relation between the duration of remission and hyperglycemia during induction chemotherapy for acute lymphocytic leukemia with a hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone / methotrexate-cytarabine regimen. Cancer. 100 (6): 1179-1185
1469. Weisburger, J. H., Reddy, B. S., Rose, D. P., Cohen, L. A., Kendall, M. E. and Wynder, E. L. 1993. Protective mechanisms of dietary fibers in nutritional carcinogenesis. Basic Life Sci. 61: 45-63, PMID: 8304953

1470. Weiss, J. M., Davies, L. C., Karwan, M., Ileva, L., Ozaki, M. K., Cheng, R. Y. S., Ridnour, L. A., Annunziata, C. M., Wink, D. A. and McVicar, D. W. 2018. Itaconic acid mediates crosstalk between macrophage metabolism and peritoneal tumors. J Clin Invest. 128(9): 3794-3805

1471. Weiss, J., Theile, D., Ketabi-Kiyanvash, N., Lindenmaier, H. and Haefeli, W. E. 2007. Inhibition of MRP1/ABCC1, MRP2/ABCC2 and MRP3/ABCC3 by nucleoside, nucleotide, and non-nucleoside reverse transcriptase inhibitors. Drug Metab Dispos. 35(3): 340-4

1472. Weitsman, G. E., Ravid, A., Liberman, U. A. and Koren, R. 2003. Vitamin D enhances caspase-dependent and independent TNF-induced breast cancer cell death: the role of reactive oxygen species. Ann N Y Acad Sci. 1010: 437-40, doi: 10.1196/annals.1299.079

1473. Wen, J., Fu, A. F., Chen, L. J., Xie, X. J., Yang, G. L., Chen, X. C., Wang, Y. S., Li, J., Chen, P., Tang, M. H., Shao, X. M., Zhao, X. and Wei, Y. Q. 2009. Liposomal honokiol inhibits VEGF-D-induced lymphangiogenesis and metastasis in xenograft tumor model. Int J Cancer. 124(11): 2709-18

1474. Wendling, D., Abbas, W., Godfrin-Valnet, M., Guillot, X., Khan, K.A., Cedoz, J.P., Baud, L., Prati, C and Herbein, G. 2013. Resveratrol, a sirtuin 1 activator, increases IL-6 production by peripheral blood mononuclear cells of patients with knee osteoarthritis. Clin Epigenetics. 5(1):10, doi: 10.1186/1868-7083-5-10, 7 pages

1475. Wesolowska, O., Wisniewski, J., Sroda, K., Krawczenko, A., Bielawska-Pohl, A., Paprocka, M., Dus, D. and Michalak, K. 2010. 8-Prenylnaringenin is an inhibitor of multidrug resistance-associated transporters, 9-glycoprotein and MDR1. European Journal of Pharmacology. 644: 32-40, doi: 10.1016 / j.ejphar. 2010.06.069

1476. West, S. A., Viswanathan, S. R., Yabuuchi, A., Cunniff, K., Takeuchi, A., Park, I. H., Sero, J. E., Zhu, H., Perez-Atayde, A., Frazier, A. L., Surani, M. A. and Daley, G. Q. 2009. A role for Lin28 in primordial germ-cell development and germ-cell malignancy. Nature. 460(7257): 909-13

1477. West, W. P., Parker, C. L., Ward, R. J. and Sabroe, I. 2008. Differential and cell-type specific regulation of responses to Toll-like receptor agonists by ISO-1. Immunology. 125(1): 101-110, https://doi.org/10.1111/j.1365-2567.2008.02825.x

1478. Westra, J., Limburg, P. C., de Boer, P. and van Rijswijk, M. H. 2004. Effects of RWJ67657, a p38 mitogen activated protein kinase (MAPK) inhibitor, on the production of inflammatory mediators by rheumatoid synovial fibroblasts. Ann Rheum Dis. 63: 1453-1459, doi: 10.1136/ard.2003.013011

1479. White, J. R., Lee, J. M., Young, P. R., Hertzberg, R. P., Jurewicz, A. J., Chaikin, M. A., Widdowson, K., Foley, J. J., Martin, L. D., Griswold, D. E. and Sarau, H. M. 1998. Identification of a potent selective non-peptide CXCR2 antagonist that inhibits interleukin-8-induced neutrophil migration. J Biol Chem. 273(17): 10095-8

1480. Whitehouse, D. B., Pilz, A. J., Porta, G. and Hopkinson, D. A. 1988. Rhodanese iso enzymes in human tissues. Ann Hum Genet. 52 (1): 1-10, PMID: 3178139

1481. Wilhelm, S. M., Adnane, L., Newell, P., Villanueva, A., Llovet, J. M. and Lynch, M. 2008. Preclinical overview of sorafenib, a multikinase inhibitor that targets both Raf and VEGF and PDGF receptor tyrosine kinase signaling. Molecular Cancer Therapeutics. 7(10): 3129-40

1482. Williams, A. S., Chen, L., Kwon, H., Fenard, D., Bisgrove, D., Verdin, E. and Greene, C. W. 2004. Prostratin antagonizes HIV latency by activating NF-kB. The Journal of Biological Chemistry. 279(40): 42008-42017

1483. Wilson, T. R., Wang, J., Chinchilli, V., Richie, J. P., Virtamo, J., Moore, L. E. and Albanes, D. 2009. Fish, vitamin D and flavonoids in relation to renal cell cancer among smokers. Am J Epidemiol. 170(6): 717-729

1484. Winnicka, K., Bielawski, K., Bielawska, A. and Miltyk, W. 2007. Apoptosis-mediated cytotoxicity of ouabain, digoxin and proscillaridin A in the estrogen independent MDA-MB-231 breast cancer cells. Arch Pharm Res. 30(10): 1216-1224

1485. Wise, D. R. and Thompson, C. B. 2010. Glutamine addiction: a new therapeutic target in cancer. Trends Biochem Sci. 35(8): 427-433

1486. Wodinsky, I. and Swiniarski, J. K. 1975. Antitumor activity of amygdalin MF(NSC-15780) as a single agent and with beta-glucosidase (NSC-128056) on a spectrum of transplantable rodent tumors. Cancer Chemother Rep. 59(5): 939-50

1487. Woltowicz-Praga, S. M., Dickson, R. B. and Hawkins, M. J. 1997. Matrix metalloproteinase inhibitors. Invest New Drugs. 15(1): 61-75 PMID:9195290

1488. Wong, P., Cuello, C., Bertouch, J. V., Roberts-Thompson, P. J., Ahern, M. J., Smith, M. D. and Youssef, P. P. 2000. The effects of pulse methylprednisolone on matrix metalloproteinase and tissue inhibitor of metalloproteinase-1 expression in rheumatoid arthritis. Rhuematology. 39(10):1067-73

1489. Woo, Y., Oh, J. and Kim, J. 2017. Suppression of Nrf2 activity by chestnut leaf extract increases chemosensitivity of breast cancer stem cells to paclitaxel. Nutrients. 9(7): 760, doi: 10.3390/ nu9070760, 15 pages

1490. Wood, J. M. 2000. Inhibition of vascular endothelial growth factor (VEGF) as a novel approach for cancer therapy. Medicina. 60 (Supl 11): 41-47

1491. Woodson, K., Albanes, D., Tangrea, A. J., Rautalahti, M. and Virtamo, J. 1999. Association between alcohol and lung cancer in the alpha-tocopherol, beta carotene cancer prevention study in Finland. Cancer Causes and Control. 10(3): 219-226

1492. Wrobel, A., Eklund, P., Bobrowska_Hagerstrand, M. and Hagerstrand, H. 2010. Lignans and norlignans inhibit multidrug resistance protein 1 (MRP1/ABCC1)-mediated transport. Anticancer Research. 30(11): 4423-4428

1493. Wu, H., Chen, J., Yuan, M., Xu, G. and Lin, S. 2016. Effects of sulforaphane on TNF-α-induced pro-inflammatory cytokine production and reactive oxygen species generation in mouse brain endothelial cells. Int J Clin Exp Med. 9(2): 4929-4938

1494. Wu, H., Lin, S. and Chen, Y. 2005. Inhibition of cell proliferation and in vitro markers of angiogenesis by Indol-3-carbinol, a

major indole metabolite present in cruciferous vegetables. J Agric Food Chem. 53: 5164-5169, doi: 10.1021/jfo50034w

1495. Wu, J. W., Wang, J. J., Chen, J. B., Huang, Y. L., Wang, H., Liu, G. H., Li, L. F., Kang, M., Wang, X. G. and Cai, H. H. 2015. Resveratrol could reverse the expression of SIRT1 and MMP-1 in vitro. Genet Mol Res. 14(4): 12386-93

1496. Wu, L., Lu, H. and Chou, Y. 2015. Kaempferol induces DNA damage and inhibits DNA repair associated protein expressions in human promyelocytic leukemia HL-60 cells. The American Journal of Chinese Medicine. 43(2): 365-82

1497. Wu, L., Zhang, Y., Ma, X., Zhang, N. and Qin, G. 2012. The effect of resveratrol on Foxo1 expression in kidneys of diabetic nephropathy rats. Molecular Biology Reports. 39(9): 9085-9093

1498. Wu, M., Lien, G., Shen, S., Yang, L. and Chen, Y. 2013. HSP90 inhibitors, geldanamycin and radicicol, enhance fisetin-induced cytotoxicity via induction of apoptosis in human colonic cancer cells. Evidence-Based Complementary and Alternative Medicine. Vol.2013. Article ID 987612, doi: 10.1155/2013/987612, 11 pages

1499. Wu, P., Yen, J., Kou, M. and Wu, M. 2015. Luteolin and apigenin attenuate 4-hydroxy-2-nonenal-mediated cell death through modulation of UPR, Nrf2-ARE and MAPK pathways in PC12 cells. PLos One. 10(6): e0130599, doi: 10.1371/journal. pone.0130599, 23 pages

1500. Wu, S. J. and Ng, L. T. 2007. Tetrandrine inhibits proinflammatory cytokines, INOS and COX-2 expression in human monocytic cells. Biol Pharm Bull. 30(1): 59-62, PMID: 17202660

1501. Wu, T., Jia, J., Xiong, X., He, H., Bu, L., Zhao, Z., Huang, C. and Zhang, W. 2013. Increased expression of Lin28B associates with poor prognosis in patients with oral squamous cell carcinoma. Plos One. 8(12): e83869, doi: 10. 1371/journal.pone.0083869, 9 pages

1502. Wu, Y., Cain-Hom, C., Choy, L., Hagenbeek, T. J., de Leon, G. P., Chen, Y., Finkle, D-, Venook, R., Wu, X., Ridgway, J., Schahin-Reed, D., Dow, G. J., Shelton, A., Stawicki, S., Watts, R. J., Zhang, J., Choy, R., Howard, P., Kadyk, L., Yan, M., Zha, J., Callahan, C. A., Hymowitz, S. G. and Siebel, C. W. 2010.

Therapeutic antibody targeting of individual Notch receptors. Nature. 464: 1052-1059, doi: 10.1038/nature08878

1503. Wu, Y., Zhang, Z., Liao, X. and Wang, Z. 2015. High fat diet triggers cell cycle arrest and excessive apoptosis of granulose cells during the follicular development. Biochem Biophys Res Commun. 466(3): 599-605

1504. Xi, J., Chen, Y., Huang, S., Cui, F. and Wang, X. 2018. Suppression of GRP78 sensitizes human colorectal cancer cells to oxaliplatin by down-regulation of CD-24. Oncology Letters. 15(16): 9861-9867

1505. Xi, Q., Gao, N., Yang, Y., Ye, W., Zhang, B., Wu, J., Jiang, G. and Zhang, X. 2015. Anticancer drugs induce hypomethylation of the acetylcholine-esterase promoter via a phosphorylated-p38-DNMT1-AChE pathway in apoptotic hepatocellular carcinoma cells. The International Journal of Biochemistry & Cell Biology. 68:21-32, http://dx.doi.org/10.1016/j.biocel.2015.08.013

1506. Xia, C., Bai, X., Hou, X., Gou, X., Wang, Y., Zeng, H., Huang, M. and Jin, J. 2015. Cryptotanshinone reverses cisplatin resistance of human lung carcinoma A549 cells through down-regulating Nrf2 pathway. Cell Physiol Biochem. 37(2): 816-24

1507. Xia, Y., Shen, S. and Verma, M. I. 2014. NF-kB, an active player in human cancers. Cancer Immunol Res. 2(9): 823-830

1508. Xia, Z., Luo, T., Liu, H. M., Wang, F., Xia, Z. Y., Irwin, M. G.and Vanhoutte, P. M. 2010. L-arginine enhances nitrative stress and exacerbates tumor necrosis factor-alpha toxicity to human endothelial cells in culture: prevention by propofol. J Cardiovasc Pharmacol. 55(4): 358-67

1509. Xiao, G., Li, X., Li, G., Zhang, B., Xu, C., Qin, S., Du, N., Wang, J., Tang, S., Zhang, J., Ren, H., Chen, K. and Sun, X. 2017. MiR-129 blocks estrogen induction of Notch signaling activity in breast cancer stem-like cells. Oncotarget. 8(61): 103261-103273

1510. Xiao, H. B., Lu, X. Y., Liu, Z. K. and Luo, Z. F. 2016. Kaempferol inhibits the production of ROS to modulate OPN-αvβ3 integrin pathway in HUVECs. J Physiol Biochem. 72(2): 303-13

1511. Xiao, R. Z., Chen, Y., Wang, L. L., Ruan, X. X., He, C. M., Xiong, M. J. and Lin, D. J. 2011. Sorafenib induces apoptosis of

U937 cells via inhibiting WNT signal pathway. Zhonqquo Shi Yan Xue Ye Xue Za Zhi. 19(2): 353-7

1512. Xiao, X., Shi, D., Liu, L., Wang, J., Xie, X., Kang, T. and Deng, W. 2011. Quercetin suppresses cyclooxygenase-2 expression and angiogenesis through inactivation of P300 signaling. Plos One. 6(8): e22934, doi: 10.1371/journal.pone.0022934, 10 pages

1513. Xiaodan, W., Yongping, Y., Liu, Y., Mu, L. and Xiuhui, Z. 2016. Effect of quercetin on the expression of Bcl-2/Bax apoptotic proteins in endometrial cells of lipopolysaccharide-induced-abortion mice. Journal of Traditional Chinese Medicine. 36(6): 737-742

1514. Xie, C., Freeman, M. J., Lu, H., Wang, X., Forster, C. L., Sarver, A. L. and Hallstrom, T. C. 2017. Retinoblastoma cells activate the Akt pathway and are vulnerable to the PI3K/mTOR inhibitor NVP-BEZ235. Oncotarget. 8(24): 38084-38098

1515. Xie, J., Johnson, R. L., Zhang, X., Bare, J. W., Waldman, F. M., Cogen, P. H., Menon, A. G., Warren, R. S., Chen, L., Scott, M. P. and Epstein, Jr. E. H. 1997. Mutations of the patched gene in several types of sporadic extracutaneous tumors. Cancer Res. 57(12): 2369-2372

1516. Xin, P., Li, C., Zheng, Y., Peng, Q., Xiao, H., Huang, Y. and Zhu, X. 2017. Efficacy of the dual PI3K and mTOR inhibitor NVP-BEZ235 in combination with imatinib mesylate against chronic myelogenous leukemia cell lines. Drug Des Devel Ther. 14: 1115-1126, doi: 10.2147/DDDT.S132092

1517. Xiong, L., Chen, Y., Tong, J., Gong, Y., Huang, J. and Liu, Z. 2018. Epigallocatechin-3-gallate promotes healthy lifespan through mitohormesis during early-to-mid adulthood in Caenorhabditis elegans. Redox Biology. 14: 305-315, https://doi.org/10.1016/j.redox.017.09.019

1518. Xu, D., Jin, J., Yu, H., Zhao, Z., Ma, D., Zhang, C. and Jiang, H. 2017. Chrysin inhibited tumor glycolysis and induced apoptosis in hepatocellular carcinoma by targeting hexokinase-2. J Exp Clin Cancer Res. 36:44, doi: 10.1186/s13046-017-0514-4, 11 pages

1519. Xu, J. Q., Chen, B., Hu, H. X., Yue, R. C., Zhang, S., Xu, L., Wang, H., Li, Q., Tan, C. Y., Chen, H. Y. and Zhang, R. Y.

2016. Lycopene protects against hypoxia/reoxygeration injury in mouse cardiomyctes by inhibiting endoplasmic reticulum stress induced apoptosis. Zhonghua Xin Xue Guan Bing Za Zhi. 44(6): 518-23

1520. Xu, L., Zhang, L., Bertucci, A. M., Pope, R. M. and Datta, S. K. 2008. Apigenin, a dietary flavonoid, sensitizes human T cells for activation-induced cell death by inhibiting PKB/Akt and NF-kB activation pathway. Immunol Lett. 121(1): 74-83, doi: 10.1016/j.imlet.2008.08.004

1521. Xu, M., Yang, H., Zhang, Q., Lu, P., Feng, Y., Geng, X., Zhang, L. and Jia, X. 2017. Oncotarget. Alpha-tocopherol prevents esophageal squamous cell carcinoma by modulating PPARY-Akt signaling pathway at the very early stage of carcinogenesis. Oncotarget. 8(56): 95914-95930

1522. Xu, X. H., Zhao, C., Peng, Q., Xie, P. and Liu, Q.H. 2017. Kaempferol inhibited VEGF and PGF expression and in vitro angiogenesis of HRECs under diabetic-like environment. Brazilian Journal of Medical and Biological Research. 50(3): e5396, 7 pages, http://dx.doi.org/10.1590/1414-431X20165396

1523. Xu, X., Bao, Z., Liu, Y., Jiang, K., Zhi, T., Wang, D., Fan, L., Liu, N. and Ji, J. 2018. PBX3/MEK/ERK1/2/LIN28/let-7b positive feedback loop enhances mesenchymal phenotype to promote glioblastoma migration and invasion. J Exp Clin Cancer Res. 37: 158, doi: 10.1186/s13046-018-0841-0, 17 pages

1524. Xu, X., Zhang, X., Zhang, Y., Yang, L., Liu, Y., Huang, S., Lu, L., Kong, L., Li, Z., Guo, Q. and Zhao, L. 2017. Wogonin reversed resistant human myelogenous leukemia cells via inhibiting Nrf2 signaling leukemia cells via inhibiting Nrf2 signaling by STAT3/NF-kB inactivation. Sci Rep. 7: 39950, doi: 10.1038/srep39950, 16 pages

1525. Yamagata, K., Daitoku, H., Takahashi, Y., Namiki, K., Hisatake, K., Kako, K., Mukai, H., Kasuya, Y. and Fukamizu, A. 2008. Arginine methylation of Foxo transcription factors inhibits their phosphorylation by Akt. Mol Cell. 32(2): 221-31

1526. Yamagata, K., Tanaka, N., Matsufuji, H. and Chino, M. 2012. B-carotene reverses the IL-1B-mediated reduction

in paraoxonase-1 expression via induction of the CaMKKII pathway in endothelial cells. Microvascular Research. 84(3): 297-305

1527. Yamamoto, H., Kishida, S., Kishida, M., Ikeda, S., Takada, S. and Kikuchi, A. 1999. Phosphorylation of axin, a Wnt signal negative regulator, by glycogen synthase kinase-3beta regulates its stability. J Biol Chem. 274(16): 10681-4

1528. Yamamoto, K., Mizumoto, A., Nishimura, K., Uda, A., Mukai, A., Yamashita, K., Kume, M., Makimoto, H., Bito, T., Nishigori, C., Nakagawa, T., Hirano, T. and Hiari, M. 2014. Association of toxicity of sorafenib and sunitinib for human keratinocytes with inhibition of signal transduction and activator of transcription 3 (STAT3). Plos One. 9(7): e102110, 7 pages, doi: 10.1371/journal.pone.0102110.g001

1529. Yamamoto, T., Fujiwara, K., Tsubota, Y., Kageyama-Yahara, N., Hayashi, S. and Kadowaki, M. 2016. Induction of regulatory T cells as a novel mechanism underlying the therapeutic action of Kakkonto, a traditional Japanese herbal medicine, in murine food allergy model. Int Arch Allergy Immunol. 169(3): 146-56

1530. Yan, M. 2011. Therapeutic promise and challenges of targeting DLL4/NOTCH1. Vascular Cell. 3: 17, doi: 10.1186/2045-824X-3-17, 5 pages

1531. Yan, M. and Nuriding, H. 2014. Reversal affect of vitamin D on different multidrug-resistant cells. Genetics and Molecular Research. 13(3): 6239-6247

1532. Yan, S., Zhang, P., Xu, W., Liu, Y., Wang, B., Jiang, T., Hua, C., Wang, X., Xu, D. and Sun, B. 2015. Serum uric acid increases risk of cancer incidence and mortality: A systematic review and meta-analysis. Mediators of Inflammation. Volume 2015. Article ID 764250, 7 pages, http://dx.doi.org/10.1155/2015/764250

1533. Yang, B., Zhao, Y., Lou, C. and Zhao, H. 2016. Eupalinolide O, a novel sesquiterpene lactone from *Eupatorium lindleyanum* DC., induces cell cycle arrest and apoptosis in human MDA-MB-468 breast cancer cells. Oncology Reports. 36(5): 2807-2813

1534. Yang, F., Jove, V., Buettner, R., Xin, H., Wu, J., Wang, Y., Nam, S., Xu, Y., Ara, T., DeClerck, Y. A., Seeger, R., Yu, H. and Jove,

R. 2012. Sorafenib inhibits endogenous and IL-6/S1P induced JAK2-STAT3 signaling in human neuroblastoma associated with growth suppression and apoptosis. Cancer Biol Ther. 13(7): 534-41

1535. Yang, H., Chang, H., Lee, J., Kim, Y., Kim, H., Lee, M., Shin, M., Ham, D., Park, H., Lee, H. and Kim, C. 2007. Amygdalin suppresses lipopolysaccharide-induced expressions of cyclooxygenase-2 and inducible nitric oxide synthase in mouse BV2 microglial cells. 29 (Supl 1): S59-S64), doi: 10.1179 / 016 / 64107X172248

1536. Yang, J. and Liu, R. H. 2009. Induction of phase II enzyme, quinine reductase, in murine hepatoma cells in vitro by grape extracts and selected phtochemicals. Food Chemistry. 114(3): 898-904

1537. Yang, J., He, J., Wang, J., Cao, Y., Ling, J., Qian, J., Lu, Y., Li, H., Zheng, Y., Lan, Y., Hong, S., Matthews, J., Starbuck, W. M., Navone, Z. R., Lin, P., Kwak, W. L. and Yi, Q. 2012. Constitutive activation of p38 MAPK in tumor cells contributes to osteolytic bone lesions in multiple myeloma. Leukemia. 26(9): 2114-2123

1538. Yang, J., Pi, C. and Wang, G. 2018. Inhibition of PI3K/ Akt/mTOR pathway by apigenin induces apoptosis and autophagy in hepatocellular carcinoma cells. Biomedicine & Pharmacotherapy. 103: 699-707, https://doi.org/10.1016/j. biopha.2018.04.072

1539. Yang, M., Teng, S., Ma, C., Yu, Y., Wang, P. and Yi, C. 2018. Ascorbic acid inhibits senescence in mesenchymal stem cells through ROS and AKT/mTOR signaling. Cytotechnology. 70(5): 1301-1313

1540. Yang, N., Zhang, H., Cai, X. and Shang, Y. 2018. Epigallocatechin-3-gallate inhibits inflammation and epithelial-mesenchymal transition through the PI3K/Akt pathway via upregulation of PTEN in asthma. Int J Mol Med. 41(2):818-828

1541. Yang, W. S., Moon, S. Y., Lee, M. J. and Park, S. 2016. Epigallocatechin-3-gallate attenuates the effects of TNF-α in vascular endothelial cells by causing ectodomain shedding of TNF receptor 1. Cellular Physiology and Biochemistry. 38: 1963-1974, doi: 10.1159/000445557

1542. Yang, W. S., Moon, S. Y., Lee, M. J. and Park, S. K. 2016. Epigallocatechin-3-gallate attenuates the effects of TNF-α in vascular endothelial cells by causing ectodomain shedding of TNF receptor 1. Cell Physiol Biochem. 38(5): 1963-74
1543. Yang, W., Luo, Y., Aisa, H. A., Xin, X., Totahon, Z., Mao, Y., Hu, M., Xu, L. and Zhang, R. 2012. Hepatoprotective activities of a sesquiterpene-rich fraction from the aerial part of Cichorium glandulosum. Chinese Medicine. 7:21, http://www.cmjournal.org/content/7/1/21, 7 pages.
1544. Yang, Y. and Bedford, M. T. 2012. Protein arginine methyltransferases and cancer. Nature Reviews Cancer. 13: 37-50, https://doi.org/10.1038/nrc3409
1545. Yang, Y. M., Yang, Y., Dai, W. W., Li, X. M., Ma, J. Q. and Tang, L. P. 2016. Genistein-induced apoptosis is mediated by endoplasmic reticulum stress in cervical cancer cells. European Review for Medical and Pharmacological Sciences. 20(15): 3292-3296
1546. Yang, Y., Guo, J. X., Shao, Z. Q. and Gao, J. P. 2017. Matrine inhibits bladder cancer cell growth and invasion in vitro through PI3K/AKT signaling pathway: An experimental study. Asian Pac J Trop Med. 10(5): 515-519
1547. Yang, Y., Shao, Z. and Guo, J. 2017. Sunitinib inhibits renal cell growth and invasion in vitro through Wnt/β-catenin signaling pathway: an experimental study. Journal of Hainan Medical University. 23(8): 31-34
1548. Yao, C., Yang, C., Chuang, S., Yan, J., Liu, C., Chen, S., Yan, K., Lai, T. and Lai, G. 2011. Targeting PML-RARα and oncogenic signaling pathways by Chinese herbal mixture tien-hsien liquid in acute promyelocytic leukemia NB4 cells. Evidence-Based Complementary and Alternative Medicine. 2011: 98415, doi: 10.1093/ecam/nep165, 11 pages
1549. Yao, K., Yin, Y., Chu, W., Liu, Z., Deng, D., Li, T., Huang, R., Zhang, J., Tan, B., Wang, W. and Wu, G. 2008. Dietary arginine supplementation increases mTOR signaling activity in skeletal muscle of neonatal pigs. The Journal of Nutrition. 138(5): 867-72
1550. Yao, M., Shang, Y., Zhou, Z., Yang, Y., Wu, Y., Guan, L., Wang, X., Zhou, S. and Wei, X. 2017. The research on lapatinib in

autophagy cell cycle arrest and epithelial to mesencyhymal transition via Wnt/Erk/PI3K-AKT signaling pathway in human cutaneous cell carcinoma. J Cancer. 8(2): 220-226

1551. Yao, Y., Jones, E. and Inoki, K. 2017. Lysosomal regulation of mTORC1 by amino acids in mammalian cells. Biomolecules. 7(3): 51-69

1552. Yap, T. A., Walton, M. I., Grimshaw, K. M., Te Poele, R. H., Eve, P. D., Valenti, M. R., de Haven, B. A. K., Martins, V., Zetterlund, A., Heaton, S. P., Heinzmann, K., Jones, P. S., Feltell, R. E., Reule, M., Woodhead, S. J., Davies, T. G., Lyons, J. F., Raynaud, F. I., Eccles, S. A., Workman, P., Thompson, N. T. and Garrett, M. D. 2012. AT13148 is a novel, oral multi-AGC kinase inhibitor with potent pharmacodynamic and antitumor activity. Clin Cancer Res. 18(14): 3912-23

1553. Yap, T. A., Walton, M. I., Hunter, L. J., Valenti, M., de Haven, B. A., Eve, P. D., Ruddle, R., Heaton, S. P., Henley, A., Pickard, L., Vijayaraghavan, G., Caldwell, J. J., Thompson, N. T., Aherne, W., Raynoud, F. I., Eccles, S. A., Workman, P., Collins, I. and Garrett, M.D. 2011. Preclinical pharmacology, antitumor activity and development of pharmacodynamic markers for the novel, potent Akt inhibitor CCT128930. Mol Cancer Ther. 10(2): 360-71

1554. Yavropoulou, M. P., Maladaki, A. and Yovos, J. G. 2015. The role of Notch and Hedgehog signaling pathways in pituitary development and pathogenesis of pituitary adenomas. Hormones (Athens). 14(1): 5-18, doi: 10.1007/BF03401377

1555. Ye, M., Wu, Q., Zhang, M. and Huang, J. 2016. Lycopene inhibits the cell proliferation and invasion of human head and neck squamous cell carcinoma. Mol Med Rep. 14(4): 2953-2958

1556. Ye, M., Zhang, J., Zhang, J., Miao, Q., Yao, L. and Zhang, J. 2015. Curcumin promotes apoptosis by activating the p53-miR-192-5p/215-XIAP pathway in non-small cell lung cancer. Cancer Lett. 357(1): 196-205, doi: 10.1016/j.canlet.2014.11.028

1557. Ye, X., Xu, G., Chang, Q., Fan, J., Sun, Z., Qin, Y. and Jiang, A. C. 2010. ERK1/2 signaling pathways involved in VEGF release in diabetic rat retina. Invest Ophthalmol Vis Sci. 51(10):5226-33

1558. Ye, Y., Wang, H., Chu, J., Chou, G. and Yu, Z. 2011. Activation of p38 MAPK pathway contributes to the melanogenic property of apigenin in B16 cells. Experimental Dermatology. 20(9): 755-757
1559. Yeh, C. and Yen, G. 2005. Effect of sulforaphane on metallothionein expression and induction of apoptosis in human hepatoma HepG2 cells. Carcinogenesis. 26(12): 2138-2148
1560. Yeh, C., Pai, M., Li, C., Tasi, Y. and Yeh, S. 2010. Effect of arginine on angiogenesis induced by human colon cancer: in vitro and in vivo studies. The Journal of Nutritional Biochemistry. 21(6): 528-543
1561. Yen, W. C., Fischer, M. M., Axelrod, F., Bond, C., Cain, J., Cancilla, B., Henner, W. R., Meisner, R., Sato, A., Shah, J., Tang, T., Wallace, B., Wang, M., Zhang, C., Kapoun, A. M., Lewicki, J., Gurney, A. and Hoey, T. 2015. Targeting Notch signaling with a Notch2/Notch3 antagonist (tarextumab) inhibits tumor growth and decreases tumor-initiating cell frequency. Clin Cancer Res. 21(9): 2084-95
1562. Yin, X., Li, Y. W., Jin, J. J., Zhou, Y., Ren, Z. G., Qiu, S. J. and Zhang, B. H. 2013. The clinical and prognostic implications of pluripotent stem cell gene expression in hepatocellular carcinoma. Oncol Lett. 5(4): 1155-1162
1563. Yoon, J. H., Cho, M. L., Back, J. Y., Park, M. K., Lee, S. W., Choi, B. J., Ashktorab, H., Smoot, D. T., Nam, S. W., Lee, J. Y. and Park, W. S. 2013. Gastrokine 1 regulates NF-kB signaling pathway and cytokine expression in gastric cancers. J Cell Biochem. 114(8): 1800-1809
1564. Yoon, J. S., Lee, H. J., Choi, S. H., Chang, E., Lee, S. Y. and Lee, E. J. 2011. Quercetin inhibits IL-1B-induced inflammation, hyaluronan production and adipogenesis in orbital fibroblasts from graves' orbitopathy. PlosOne. 6(10): e26261, 10 pages, https://doi.org/10.1371/journal.pone.0026261
1565. Yoshida, N., Koizumi, M., Adachi, I. and Kawakami, J. 2006. Inhibition of P-glycoprotein mediated transport by terpenoids contained in herbal medicines and natural products. Food and Chemical Toxicology. 44(12): 2033-2039
1566. You, S., Li, R., Park, D., Xie, M., Sica, G. L., Cao, Y., Xiao, Z. Q. and Deng, X. 2014. Disruption of STAT3 by niclosamide

reverses radioresistance of human lung cancer. Mol Cancer Ther. 13(3): 606-16

1567. Youn, S. G., Kwon, D., Ju, M. S., Rhim, H., Bae, S. Y., Choi, Y. S. and Park, J. 2014. Celastrol ameliorates HIV-1 Tat-induced inflammatory responses via induction in astrocytes. Toxicology and Applied Pharmacology. 280(1): 42-52, doi: 10.1016/j.taap.2014.07.010

1568. Young, L. C., Listgarten, J., Trotter, M. J., Andrew, S. E. and Tron, V. A. 2008. Evidence that dysregulated DNA mismatch repair characterizes human nonmelanoma skin cancer. Br J Dermatol. 158(1): 59-69, https://doi.org/10.1111/j.1365-2133.2007.08249.x

1569. Youngblood, V. M., Kim, L. C., Edwards, D. N., Hwang, Y., Santapuram, P. R., Stirdivant, S. M., Lu, P., Ye, F., Brantley-Sieders, D. M. and Chen, J. 2016. The ephrin-A1/EPHA2 signaling axis regulates glutamine metabolism in HER2-posirtive breast cancer. Cancer Research. 76(7): 825-36

1570. Yu, D., Shin, H., Lee, Y. S., Lee, D., Kim, S. and Lee, C. Y. 2014. Genistein attenuates cancer stem cell characteristics in gastric cancer through the downregulation of Gli1. Oncology Reports. 31: 673-678. DOI: 10.3892/or.2013.2893, 9 pages

1571. Yu, D., Macdonald, J., Liu, G., Lee, A. S., Ly, M., Davis, T., Ke, N., Zhou, D., Wong-Staal, F. and Li, Q. 2008. Pyrvinium targets the unfolded protein response to hypoglycemia and anti-tumor activity is enhanced by combination therapy. Plos One. 3(12): e3951, doi: 10.1371/journal.pone.0003951

1572. Yu, J., Zhou, P., Asenso, J., Yang, X., Wang, C. and Wei, W. 2016. Advances in plant-based inhibitors of P-glycoprotein. Journal of Enzyme Inhibition and Medicinal Chemistry. 31(6): 867-881

1573. Yu, P., Laird, D., Du, X., Wu, J., Won, K., Yamaguchi, K., Hsu, P. P., Qian, F., Jaeger, C.T., Zhang, W., Buhr, C. A., Shen, P., Abulafia, W., Chen, J., Young, J., Plonowski, A., Yakes, F. M., Chu, F., Lee, M., Bentzien, F., Lam, S. T., Dale, S., Matthews, D. J., Lamb, P. and Foster, P. 2014. Characterization of the activity of the PI3K/mTOR inhibitor XL765 (SAR245409) in tumor models with diverse genetic alterations affecting the PI3K pathway. Mol Cancer Ther. 13(5): OF1-OF14, doi: 10.1158/1135-7163. MCT-13-0709

1574. Yu, S., Chen, T., Tseng, S. and Chen, Y. 2007. Tryptanthrin inhibits MDR1 and reverses doxorubicin resistance in breast cancer cells. Biochemical and Biophysical Research Communications. 358(1): 79-84, doi: 10.1016/j.bbrc.2007.04.107

1575. Yu, S., Jeong, H., Jung, J. and Kim, S. 2013. Sulforaphane (SFN) regulates dedifferentiation and cyclooxygenase-2 (COX-2) expression via MAPkinase pathway in rabbit articular chondrocytes. Biomedicine & Preventive Nutrition. 3(1):91-97, doi:10.1016/j.bionut. 2012.10.012

1576. Yu, S., Wang, Z., Su, Z., Song, J., Zhou, L., Sun, Q., Liu, S., Li, S., Li, Y., Wang, M., Zhang, G., Zhang, X., Liu, Z. and Lu, D. 2018. Gigantol inhibits Wnt/β-catenin signaling and exhibits anticancer activity in breast cancer cells. BMC Complement Altern Med. 18: 59, doi: 10.1186/s12906-018-2108-x, 8 pages

1577. Yuan, C., Horng, C., Lee, C., Chiang, N., Tsai, F., Lu, C., Chiang, J., Hsu, Y., Yang, J. and Chen, F. 2017. Epigallocatechin gallate sensitizes cisplatin-resistant oral cancer CAR cell apoptosis and autophagy through stimulating AKT/STAT3 pathway and suppressing multidrug resistance 1 signaling. Environmental Toxicology. 32(3): 845-855

1578. Yuan, L., Zhang, Y., Xia, J., Liu, B., Zhang, Q., Liu, J., Luo, L., Peng, Z., Song, Z. and Zhu, R. 2015. Resveratrol induces cell cycle arrest via a p53-independent pathway in A549 cells. Mol Med Rep. 11(4): 2459-2464

1579. Yuan, Z., Goetz, J. A., Singh, S., Ogden, S. K., Petty, W. J., Black, C. C., Memoli, V. A., Dmitrovsky, E. and Robbins, D. J. 2007. Frequent requirement of hedgehog signaling in non-small cell lung carcinoma. Oncogene. 26(7): 1046-1055

1580. Yue, C., Ji, C., Zhang, H., Zhang, L. W., Tong, J., Jiang, Y. and Chen, T. 2017. Protective effects of folic acid on PM2.5-induced cardiac developmental toxicity in zebrafish embryos by targeting Ahr and Wnt/β-catenin signal pathways. Environmental Toxicology. 32: 2316-2322, doi: 10.1002 / tox.22448

1581. Zadi Heydarabad, M., Nikasa, M., Vatanmakanian, M., Azimi, A. and Farshdousti Hagh, M. 2018. Regulatory effect of resveratrol and prednisolone on MDR1 gene expression in acute

lymphoblastic leukemia cell line (CCRF-CEM): An epigenetic perspective. J Cell Biochem. 119(6): 4890-4896

1582. Zainal, Z., Langman, A. J., Hurst, K., Duggan, B., Caterson, B., Hughes, C. E. and Harwood, J. L. 2009. Relative efficacies of omega-3 polyunsaturated fatty acids in reducing expression of key proteins in a model system for studying osteoarthritis. Osteoarthritis and Cartilage. 17(7): 896-905

1583. Zakikhani, M., Blouin, M. J., Piura, E. and Pollak, M. N. 2010. Metformin and rapamycin have distinct effects on the Akt pathway and proliferation in breast cancer cells. Breast Cancer Res Treat. 123(1): 271-9, doi: 10.1007/s10549-010-0763-9

1584. Zanotto-Filho, A., Braganhol, E., Battastini, A. M. and Moreira, J. C. 2012. Proteasome inhibitor MG132 induces selective apoptosis in glioblastoma cells through inhibition of PI3K/Akt and NFkappaB pathways. Mitochondrial dysfunction, and activation of p38-JNK1/2 signaling. Invest New Drugs. 30(6): 2252-62

1585. Zeegers, M. P. A., Goldbohm, R. A. and van den Brandt, P. A. 2001. Are retinol, vitamin C, vitamin E, folate and carotenoids intake associated with bladder cancer risk? Results from the Netherlands cohort study. British Journal of Cancer. 85(7):977-983

1586. Zeng, L., Holly, J. M. P. and Perks, C. M. 2014. Effects of physiological levels of the green tea extract epigallocatechin-3-gallate on breast cancer cells. Front Endocrinol (Lausanne). 5:61, doi:10.3389/fendo.2014.00061, 10 pages

1587. Zeng, Y. and Yang, Y. 2018. Piperine depresses the migration progression via downregulating the Akt/mTOR/MMP-9 signaling pathway in DU145 cells. Mol Med Rep. 17(5): 6363-6370

1588. Zeng, Y., Kulkami, P., Inoue, T. and Getzenberg, R. H. 2009. Down-regulating cold shock protein genes impairs cancer cell survival and enhances chemosensitivity. J Cell Biochem. 107(1): 179-188, doi: 10.1002/jcb.2214

1589. Zeng, Y., Yokohira, M., Saoo, K., Takeuchi, H., Chen, Y., Yamakawa, K., Matsuda, Y., Kakehi, Y. and Imaida, K. 2005. Inhibition of prostate carcinogenesis in probasin/SV40 T antigen

transgenic rats by raloxifene, an antiestrogen with anti-androgen action, but not nimesulide, a selective cyclooxygenase-2 inhibitor. Carcinogenesis. 26(6): 1109-1116

1590. Zeng, Y., Zhou, L., Chen, Q., Li, Y., Shao, Y., Ren, W., Liao, Y., Wang, H., Zhu, J., Huang, M., He, F., Wang, J., Wu, K. and He, B. 2017. Resveratrol inactivates PI3K/Akt signaling through upregulating BMP7 in human colon cancer cells. Oncology Reports. 38(1):456-464, https://doi.org/10.3892/or.2017.5662

1591. Zgorzynska, E., Dziedzic, B., Gorzkiewicz, A., Stukzewski, D., Bielawska, K., Su, K. and Walczewska, A. 2017. Omega-3 polyunsaturated fatty acids improve the antioxidative defense in rat astrocytes via an Nrf2-dependent mechanism. Pharmacological Reports. 69(5): 935-942

1592. Zhang, A., Pan, W., Lv, J. and Wu, H. 2017. Protective effect of amygdalin on LPS-induced acute lung injury by inhibiting NF-kβ and NLRP3 signaling pathways. Inflammation. 40(3): 745-751

1593. Zhang, C., Su, Z., Khor, T. O., Shu, L. and Kong, A. T. 2013. Sulforaphane enhances Nrf2 expression in prostate cancer TRAMP C1 cells through epigenetic regulation. Biochem Pharmacol. 85(9): 1398-1404

1594. Zhang, H., Dou, J., Yu, Y., Zhao, Y., Fan, Y., Cheng, J., Xu, X., Liu, W., Guan, S., Chen, Z., Shi, Y., Patel, R., Vasudevan, A. S., Zage, P. E., Zhang, H., Nuchtern, J. G., Kim, E. S., Fu, S. and Yang, J. 2015. mTOR ATP-competitive inhibitor INK128 inhibits neuroblastoma growth via blocking mTORC signaling. Apoptosis. 20(1): 50-62, doi: 10.1007/s10495-014-1066-0

1595. Zhang, H., Zong, Y., Qiu, G., Jia, R., Xu, X., Wang, F. and Wu, D. 2018. Silencing Lin28 promotes apoptosis in colorectal cancer cells by upregulating Let-7c targeting of antiapoptotic Bcl2l1. Mol Med Rep. 17(4): 5143-5149

1596. Zhang, J., Su, H., Li, Q., Li, J. and Zhao, Q. 2017. Genistein decreases A549 cell viability via inhibition of the PI3K/Akt/Hif-1α/VEGF and NF-kB/COX-2 signaling pathways. Medicine Reports. 15(4):2296-2302

1597. Zhang, K., Wang, X. and Wang, H. 2014. Effect and mechanism of Src tyrosine kinase inhibitor sunitinib on the drug-resistance reversal of human A549/DPP cisplatin resistant lung cancer cell line. Molecular Medicine Reports. 10(4): 2065-2072

1598. Zhang, L., Ii, L., Jiao, M., Wu, D., Wu, K., Li, X., Zhu, G., Yang, L., Wang, X., Hsieh, J. T. and He, D. 2012. Genistein inhibits the stemness properties of prostate cancer cells through targeting Hedgehog-Gli1 pathway. Cancer Lett. 323(1):48-57, doi: 10.1007/s00432-011-1146-2.

1599. Zhang, L., Ma, S., Su, H. and Cheng, J. 2018. Isoliquiritigenin inhibits IL-1β-induced production of matrix metalloproteinase in articular chondrocytes. Molecular & Clinical Development. 9:153-159, https//doi.org/10.1016/j.omtm.2018.02.006

1600. Zhang, L., Xu, X., Yang, R., Chen, J., Wang, S., Yang, J., Xiang, X., He, Z., Zhao, Y., Dong, Z. and Zhang, D. 2015. Paclitaxel attenuates renal interstitial fibroblast activation and interstitial fibrosis by inhibiting STAT3 sgnaling. Drug Des Devel Ther. 9: 2139-48, doi: 10.2147/DDDT-S81390

1601. Zhang, P., Li, H., Yang, B., Yang, F., Zhang, L. L., Kong, Q. Y., Chen, X. Y., Wu, M. L. and Liu, J. 2014. Biological significance and therapeutic implication of resveratrol-inhibited Wnt, Notch and STAT3 signaling in cervical cancer cells. Genes Cancer. 5(5-6): 154-64

1602. Zhang, Q., Li, Q., Chen, Y., Huang, X., Yang, I. H., CaO, L., Wu, W. K. and Tan, H. M. 2012. Homocyteine-impaired angiogenesis is associated with VEGF/VEGFR inhibition. Front Biosci. 4:2525-35, http://dx.doi.org/10.2741/563

1603. Zhang, S. and Morris, M. E. 2003. Effect of the flavonoids biochanin A and silymarin on the P-glycoprotein-mediated transport of digoxin and vinblastine in human intestinal Caco-2 cells. Pharm Res. 20(8): 1184-91

1604. Zhang, S., Hunter, D. J., Hankinson, S. E., Giovannucci, E. L., Rosner, B. A., Colditz, G. A., Speizer, F. E. and Willett, W. C. 1999. A prospective study of folate intake and the risk of breast cancer. JAMA. 281(17):1632-1637

1605. Zhang, W., Shu, X., Li, H., Yang, G., Cai, H., Ji, B., Gao, J., Gao, Y., Zheng, W. and Xiang, Y. 2012. Vitamin intake and liver cancer risk: a report from two cohort studies in China. JNCL-J Natl Cancer Inst. 104(15):1174-1182

1606. Zhang, X., Lee, J. E., Ma, J., Je, Y., Wu, K., Willet, W. C., Fuchs, C. S. And Giovannucci, E. L. 2012. Prospective cohort studies of vitamin B6 intake and colorectal cancer incidence:modification by time?. Cancer Epidemiol Biomarkers Prev. 21(3):560

1607. Zhang, Y. 2017. *Ganoderma lucidum* (Reishi) suppresses proliferation and migration of breast cancer cells via inhibiting Wnt/β-catenin signaling. Biochemical and Biophysical Research Communications. 488(4): 679-684

1608. Zhang, Y. Y., Long, J. R., Liu, P. Y., Liu, Y. J., Shen, H., Zhao, L. J. and Deng, H. W. 2003. Estrogen receptor alpha and vitamin D receptor gene polymorphisms and bone mineral density: association study of healthy pre-and postmenopausal Chinese women. Biochem Biophys Res Commun. 308(4): 777-83

1609. Zhang, Y., Dong, J., He, P., Li, W., Zhang, Q., Li, N. and Sun, T. 2012. Genistein inhibit cytokines or growth factor-induced proliferation and transformation phenotype in fibroblast-like synoviocytes of rheumatoid arthritis. Inflammation. 35(1): 377-87, doi: 10.1007/s10753-011-9365-x.

1610. Zhang, Y., Li, N., Caron, C., Matthias, G., Hess, D., Khochbin, S. and Matthias, P. 2003. EMBOJ. 22(5): 1168-79

1611. Zhang, Z., Li, C., Shang, L., Zhang, Y., Zou, R., Zhan, Y. and Bi, B. 2016. Sulforaphane induces apoptosis and inhibits invasion in U251MG glioblastoma cells. SpringerPlus. 5: 235, doi: 10.1186/s40064-016-1910-5, 12 pages

1612. Zhao, B., Sun, Y., Wang, S., Duan, L., Huo, Q., Ren, F. and Li, G. 2013. Grape seed procyanidin reversal of P-glycoprotein associated multi-drug resistance via down-regulation of NF-kB and MAPK/ERK mediated YB-1 activity in A2780/T cells. Plos One. 8/8:e71071, doi: 10.1371/journal.pone.0071071

1613. Zhao, C., Lu, X., Bu, X., Zhang, N. and Wang, W. 2010. Involvement of tumor necrosis factor-α in the upregulation of CXCR4 expression in gastric cancer induced by Helicobacter

pylori. BMC Cancer. 10:419, doi: 10.1186/1471-2407-10-419, 10 pages

1614. Zhao, J., He, Q., Gong, Z., Chen, S. and Cui, L. 2016. Niclosamide suppresses renal cell carcinoma by inhibiting Wnt/β-catenin and inducing mitochondrial dysfunctions. Springerplus. 5:1436, doi: 10.1186/s40064-016-3153-x, 8 pages

1615. Zhao, L., Li, H:, Shi, Y., Wang, G., Liu, L., Su, C. and Su, R. 2015. Nanoparticules inhibit cancer cell invasion and enhance antitumor efficiency by targeted drug delivery via cell surface-related GRP78. International Journal of Nanomedicine. 10: 245-256, doi: 10.2147/IJN.S74868

1616. Zhao, S., Liang, M. and Wang, Y., Hu, J., Zhong, Y., Li, J., Huang, K. and Yiging, L. 2018. Chrysin suppresses vascular endothelial inflammation via inhibiting the NF-kB signaling pathway. Journal of Cardiovascular Pharmacology and Therapeutics. Doi: 10.1177/107428418810809

1617. Zhao, W., Devamanoharan, P. S. and Varma, S. D. 1998. Fructose induced deactivation of glucose-6-phosphate dehydrogenase activity and its prevention by pyruvate: implications in cataract prevention. Free Radic Res. 29(4): 315-20

1618. Zhao, Y., Tian, B., Wang, Y. and Ding, H. 2017. Kamepferol sensitizes human ovarian cancer cells-OVCAR-3 and SKOV-3 to tumor necrosis factor-related apoptosis-inducing ligand (TRAIL): induced apoptosis via JNK/ERK-CHOP pathway and up-regulation of death receptors 4 and 5. Med Sci Monit. 23: 5096-5105, doi: 10.12659/MSM.903552

1619. Zhao, Y., Zhang, C., Zhou, W., Chen, J., Luo, N., Gong, L., Du, L. and Zhou, J. 2014. Is there a role of TNFR1 in acute lung injury cases associated with extracorporeal circulation?. J Zhejiang Univ Sci B. 15(3): 281-288

1620. Zhao, Y., Zhou, S. and Heng, C. K. 2009. Celecoxib inhibits serum amyloid a-induced matrix metalloproteinase-10 expression in human endothelial cells. J Vasc Res. 46(1): 64-72

1621. Zhao, Z., Cheng, X., Wang, Y., Han, R., Li, L., Xiang, T., He, L., Long, H., Zhu, B. and He, Y. 2014. Metformin inhibits the IL-6-induced epithelial-mesencyhmal transition and lung

adenocarcinoma growth and metastasis. Plos One. 9(4): e95884, doi: 10.1371 / journal.pone. 0095884, 12 pages

1622. Zhao, Z., Li, C., Xi, H., Gao, Y. and Xu, D. 2015. Curcumin induces apoptosis in pancreatic cancer cells through the induction of forkhead box 01 and inhibition of the PI3K/Akt pathway. Molecular Medicine Reports. 12(4): 5415-5422

1623. Zheng, A., Chen, Y., Zhao, L. and Feng, J. 2017. Myricetin induces apoptosis and enhances chemosensitivity in ovarian cancer cells. Oncol Lett. 13(6): 4974-4978

1624. Zheng, F., Tang, Q., Wu, J. J., Zhao, Y. S., Liang, Z. Y.,Li, L., Wu, W. Y. and Hun, S. 2014. p38α MAPK-mediated induction and interaction of FOXO3a and p53 contribute to the inhibited-growth and induced-apoptosis of human lung adenocarcinoma cells by berberine Journal of Experimental & Clinical Cancer Research. 33:36. https://doi.org/10.1186/1756-9966-33-36, 12 pages

1625. Zheng, F., Tang, Q., Wu, J., Zhao, S., Liang, Z. Y., Li, L., Wu, W. and Hann, S. 2014. P38α MAPK-mediated induction and interaction of Foxo3a and p53 contribute to the inhibited-growth and induced-apoptosis of human lung adenocarcinoma cells by berberine. J Exp Clin Cancer Res. 33(1): 36, doi: 10.1186/1756-9966-33-36

1626. Zheng, L., Wang, F., Li, Y., Zhang, X., Chen, L., Liang, Y., Dai, C., Yan, Y., Tao, L., Mi, Y., Yang, A., To, K. and Fu, L. 2009. Vandetanib (Zactima, ZD6474) antagonizes ABCC1-andABCG2-mediated multidrug resistance by inhibition of their transport function. PlosOne. 4(4):e5172, 9 pages, doi:10.1371/ journal.pone.0005172

1627. Zheng, W., Anderson, K. E., Kushi, L., Sellers, T. A., Greenstein, J., Hong, C., Cerhan, J. R., Bostick, R. M. and Folsom, A. R. 1998. A prospective cohort study of intake of calcium, vitamin D and other micronutrients in relation to incidence of rectal cancer among postmenopausal women. Cancer Epidemiology, Biomarkers and Prevention. 7(3): 221-225

1628. Zheng, W., Sellers, T. A., Doyle, T. J., Kushi, L. H., Potter, J. D. and Folsom, A. R. 1995. Retinol, antioxidant vitamins, and cancers of the upper digestive tract in a prospective cohort study

of postmenopausal women. American Journal of Epidemiology. 142(9): 955-960

1629. Zheng, X., Linke, S., Dias, J. M., Zheng, X., Gradin, K., Wallis, T. P., Hamilton, B. R., Gustafsson, M., Ruas, J. L., Wilkins, S., Bilton, R. L., Brismar, K., Whitelaw, M. L., Pereira, T., Gorman, J. J., Ericson, J., Peet, D. J., Lendahl, U. and Poellinger, L. 2008. Interaction with factor inhibiting HIF-1 defines an additional mode of cross-coupling between the Notch and hypoxia signaling pathways. Proc Natl Acad Sci USA. 105(9): 3368-73

1630. Zhong, H. M., Ding, Q. H., Chen, W. P. and Luo, R. B. 2013. Vorinostat, a HDAC inhibitor, showed anti-osteoarthritic activities through inhibition of iNOS and MMP expression, p38 and ERK phosphorylation and blocking NF-kB nuclear translocation. Int Immunopharmacol. 17(2): 329-35

1631. Zhong, W., Gu, B., Gu, Y., Groome, L. J., Sun, J. and Wang, Y. 2014. Activation of vitamin D receptor promotes VEGF and CuZn-SOD expression in endothelial cells. J Seroid Biochem Mol Biol. 140: 56-62, doi: 10.16/j.jsbmb. 2013.11.017

1632. Zhong, Y., Krisanapun, C., Lee, S., Nualsanit, T., Sams, C., Peungvicha, P. and Baek, S. J. 2010. Molecular targets of apigenin in colorectal cancer cells: Involvement of p21, NAG-1 and p53. Eur J Cancer. 46(18): 3365-3374

1633. Zhong, Z., Dong, Z., Yang, L., Chen, X. and Gong, Z. 2012. Inhibition of proliferation of human lung cancer cells by green tea catechins is mediated by upregulation of let-7. Exp Ther Med. 4(2): 267-272

1634. Zhou, C., Li, C., Li, D., Wang, Y., Shao, W., You, Y., Peng, J., Zhang, X., Lu, L. and Shen, X. 2013. BIG1, a brefeldin A-inhibited guanine nucleotide-exchange protein regulates neurite development via PI3K-AKT and ERK signaling pathways. Neuroscience. 254: 361-8, doi: 10.1016/j.neuroscience. 2013.09.045

1635. Zhou, H., Wang, W., Wu, G., Lee, J. and Li, A. 2007. Artesunate inhibits angiogenesis and downregulates vascular endothelial growth factor expression in chronic myeloid leukemia K562 cells. Vascular Pharmacology. 47(Issues 2-3): 131-138

1636. Zhou, L., Yao, Q., Li, Y., Huang, Y. C., Jiang, H., Wang, C. Q. and Fan, L. 2017. Sulforaphane-induced apoptosis in Xuanwei lung adenocarcinoma cell line XWLC-05. Thorac Cancer. 8(1): 16-25, doi: 10.1111/1759-7714.12396

1637. Zhou, M., Li, Z., Han, Z. and Tian, N. 2015. Paclitaxel-sensitization enhanced by curcumin involves down-regulation of nuclear factor-kB and lin28 in Hep3B cells. J Recept Signal Transduct Res. 35(6): 618-25

1638. Zhou, R., Chen, H., Chen, J., Chen, X., Wen, Y. and Xu, L. 2018. Extract from *Astragalus membranaceus* inhibit breast cancer cells proliferation via PI3K/Akt/mTOR signaling pathway. BMC Complement Altern Med. 18: 83, doi: 10.1186/s12906-018-2148-2, 8 pages

1639. Zhou, Y., Wu, Y., Jiang, X., Zhang, X., Zhang, X., Xia, L., Lin, K. and Xu, Y. 2015. The effect of quercetin on the osteogenesic differentiation and angiogenic factor expression of bone narrow-derived mesencyhymal stem cells. PlosOne. 10(6):e0129605, doi:10.1371/journal.pone.0129605, 21 pages

1640. Zhou, X., Bailey-Bucktrout, S., Jeker, L. T., Penaranda, C., Martínez-Llordella, M., Ashby, M., Nakayama, M., Rosenthal, W. and Bluestone, J. A. 2009. Foxp3 instability leads to the generation of pathogenic memory T cells *in vivo*. Nat Immunol. 10(9): 1000–1007. doi: 10.1038/ni.1774

1641. Zhu, J., Yong, W., Wu, X., Yu, Y., Iv, J., Liu, C., Mao, X., Zhu, Y., Xu, K., Han, X. and Liu, C. 2008. Anti-inflammatory effect of resveratrol on TNF-α-induced MCP-1 expression in adipocytes. Research Communications. 369(2): 471-477

1642. Zhu, J.,W., Wang, H., Chen, F., Fu, J., Xu, Y., Hou, Y., Kou, H. H., Zhoi, C., Nelson, M. B., Zhang, Q., Anderson, M. E. and Pi, J. 2016. An overview of chemical inhibitors of the Nrf2-ARE signaling pathway and their potential applications in cancer therapy. Free Radical Biology and Medicine. 99: 544-556, http://dx.doi.org/10.1016/j.freeradbiomed.2016.09.010

1643. Zhu, T., Gu, J., Yu, K., Lucas, J., Cai, P., Tsao, R., Gong, Y., Li, F., Chaudhary, I., Desai, P., Ruppen, M., Fawzi, M., Gibbons, J., Ayral-Kaloustian, S., Skotnicki, J., Mansour, T. and Zask,

A. 2006. Pegylated Wortmannin and 17-hydroxywortmannin conjugates as phosphoinositide 3-kinase inhibitors active in human tumor xenograft models. J Med Chem. 44(4): 1373-1378

1644. Zhu, W., Xu, J., Ge, Y., Cao, H., Ge, X., Luo, J., Xue, J., Yang, H., Zhang, S. and Cao, J. 2014. Epigallocatechin-3-gallate (EGCG) protects skin cells from ionizing radiation via heme oxygenase-1 (HO-1) overexpression. J Radiat Res. 55(6): 1056-1065

1645. Zhuang, C., Wu, Z., Xing, C. and Miao, Z. 2017. Small molecules inhibiting Keap1-Nrf2 protein protein interactions: a novel approach to activate. Nrf2 function. Med Chem Commun. 8: 286-294, doi: 10.1039/C6MD00500D

1646. Ziv, E., Koren, R., Zahalka, M. A. and Ravid, A. 2016. TNF-α increases the expression and activity of vitamin D receptor in keratinocytes: role of c-Jun N-terminal kinase. Dermatoendocrinol. 8(1):e1137399, doi: 10.1080/19381980.2015.1137399

1647. Zou, X., Qu, Z., Fang, Y., Shi, X. and Ji, Y. 2017. Endoplasmic reticulum stress mediates sulforaphane-induced apoptosis of HepG2 human hepatocellular carcinoma cells. Mol Med Rep. 15: 331-338, doi: 10.3892/mmr.2016.6016

1648. Zou, Y., Yang, J. and Jiang, D. 2015. Resveratrol inhibits canonical Wnt signaling in human MG-63 osteosarcoma cells. Mol Med Rep. 12(5): 7221-7226

1649. Zuris, J. A., Ali, S. S., Yeh, H., Nguyen, T. A., Nechushtai, R., Paddock, M. L. and Jennings, P. A. 2012. NADPH inhibits [2Fe-2S] cluster protein transfer from diabetes drug target MiotoNEET to an apo-acceptor protein. J Biol Chem. 287(15): 11649-55

1650. Zykova, T. A., Zhu, F., Zhai, X., Ma, W., Ermakova, S. P., Lee, K. W., Bode, A. M. and Dong, Z. 2008. Resveratrol directly targets COX-2 to Inhibit carcinogenesis. Mol Carcinog. 47(10): 797–805.



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