Review Article
Functional foods and their role in cancer prevention and health promotion: a comprehensive review

Mohammad Aghajanpour[1], Mohamad Reza Nazer[2], Zia Obeidavi[3], Mohsen Akbari[4], Parya Ezati[5], Nasroallah Moradi Kor[6]

[1]Otolaryngologist, Department of Otolaryngology Head and Neck Surgery, Lorestan University of Medical Sciences, Khorramabad, Iran; [2]MPH, Associated Professor, Department of Infectious Diseases, Lorestan University of Medical Sciences, Khorramabad, Iran; [3]Medical Student, Student Research Committee, Lorestan University of Medical Sciences, Khorramabad, Iran; [4]Young Researchers and Elite Club, Kermanshah Branch, Islamic Azad University, Kermanshah, Iran; [5]Department of Food Hygiene and Quality Control, Faculty of Veterinary Medicine, Urmia University, Urmia, Iran; [6]Young Researchers and Elite Club, Kerman Branch, Islamic Azad University, Kerman, Iran

Abstract: Following cardiovascular disease, cancer is the second leading cause of death in most affluent countries. The 13.3 million new cases of cancer in 2010 were predicted to cost US$ 290 billion, but the total costs were expected to increases to US$ 458 billion in the year 2030 on basis of World Economic Forum in 2011. More than half of all cancer cases and deaths worldwide are consider being preventable. From its inception, the disease control priorities series has focused attention on delivering efficacious health interventions that can result in dramatic reductions in mortality and disability at relatively modest cost. The approach has been multidisciplinary, and the recommendations have been evidence-based, scalable, and adaptable in multiple settings. Better and more equitable health care is the shared responsibility of governments and international agencies, public and private sectors, and societies and individuals, and all of these partners have been involved in the development of the series. Functional foods are foods and food components that supply health benefits beyond basic nutrition. It's-believed these functional foods do more than simply provide nutrients because they help to maintaining health and thereby reducing the risk of disease. There are some reported evidences showing association between functional foods and cancer. For example, S-ally cysteine of garlic and lycopene from tomatoes in combination form suppressed the development of chemically induced gastric cancer by modulation of apoptosis-associated proteins (reduced Bcl-2/Bax ratio and up-regulation of Bim and caspases 8 and 3) at considerably lower intakes than when these substances were given in isolation. Similarly, vitamin D_3 with genistein in combination form precipitated a growth inhibition of prostate cancer cells at much lower concentration than when these substances were provided individually. There are very few studies conducted worldwide to see the effects of functional foods on health or cancer or related states. This review, presents the complex patterns of cancer incidence and death around the world and evidence on effective and cost-effective ways to control cancers. The evaluation of cancer will indicate where cancer treatment is ineffective and wasteful, and offer alternative cancer care packages that are cost-effective and suited to low-resource settings. In the present paper, cancer prevention by functional foods is reviewed and the possible mechanisms of action are described.

Keywords: Apoptosis, bioactive molecule, carotenoids, genistein, prostate cancer

Introduction

A number of reactive oxygen species are produced during normal aerobic metabolism, including superoxide, hydrogen peroxide and the hydroxyl radical [1, 2]. Additionally, singlet oxygen can be produced by photochemical events (such as in the skin and eyes), and lipid peroxidation can cause to peroxyl radical formation [1, 3]. These oxidants totally participate to aging and degenerative diseases such as

cancer and atherosclerosis by oxidation of DNA, proteins and lipids [4]. Oxidation is not only reason for cancer; rather inflammation is other factor for carcinogenesis. Inflammation causes cancer by several mechanisms including the production of free radicals by inflammatory cells [5]. Cancer is a leading cause of death among adults. Cancer is one of major health problems and it is causing 1/8 deaths worldwide [6, 7]. It is estimated that about 25% of Americans will have cancer in their lifetimes.

Treatment usually involves the expensive and often traumatic use of drugs, surgery, and irradiation. The 13.3 million new cases of cancer in 2010 were predicted to cost US$ 290 billion, but the total costs were expected to increases to US$ 458 billion in the year 2030 on the basis of World Economic Forum in 2011. On the basis of these studies, more than half of all cancer cases and deaths worldwide are mostly preventable [8, 9]. Nutrition and foods are related to about 30% of all the cancers cases. There are numerous studies showing relation between functional foods and reduce in cancer [10-13]. Cancer biologists have concerned in the application of natural products to improve the survival rate of cancer patients. Americans, Japanese, and Europeans are turning to the use of dietary vegetables, medicinal herbs, and their extracts or components to prevent or treat cancer. Newly, food producers have embarked on a health criterion in the development of "functional foods", the latter being defined as food products that have an added positive health benefit [14, 15]. Functional foods are foods and food components that supply health benefits beyond basic nutrition. These foods are similar in appearance to conventional foods; functional foods consumed as part of the normal diet. Functional food supplies the body with the needed amount of vitamins, fats, proteins, carbohydrates, *etc.*, required for its healthy survival [16, 17]. Collectively, functional foods represent a continuum of items that include ingredients or natural constituents in conventional, fortified, enriched, and enhanced foods. A number of compounds naturally occurring in foods, particularly antioxidative compounds in plants or their extracts and essential oils, have shown promise as potential chemopreventive factors [18-20]. Seem antioxidants are able to reduce free radical damage to DNA which is believed to be the root cause of most cancers. It's-believed antioxidant compounds can reduce mutagenesis, and thus carcinogenesis, both by decreasing oxidative damage to DNA and by decreasing oxidant-stimulated cell division [1]. Seem astaxanthin has effectiveness at reducing the severity of several inflammatory conditions in rodents and humans. These phytonutrients include the yellow, orange and red carotenoid pigments that have recently been examined [21]. Phytochemicals divide to different groups such as carotenoids, carotenoid pigments, xanthine, lycopene's, astaxanthin and other phytochemicals. Carotenoids classified to different groups including; alcohols, hydrocarbons, ethers, epoxides, ketones, or acids functional groups. The relations between yellow, orange and red carotenoid pigments, xanthine and other phytochemical have been investigated. Of course functional foods not only involved phytochemicals, but there is other substances act similar functional foods. For example, growth factors and conditionally essential nutrients (i.e. amino acids and polyunsaturated fatty acids-PUFAs), prebiotic, probiotic and synbiotic may be benefit as ingredients in functional foods. In this study, cancer prevention by some of functional foods and the possible mechanisms of action are summarized in **Table 1**.

Astaxanthin

Structure

Astaxanthin is an alpha-hydroxyl-keto-carotenoid. It's belonging to the group of oxygenated carotenoids or xanthophylls like lutein and zeaxanthin. Astaxanthin has more hydroxyl groups than the other xanthophylls, was first discovered and identified in the year 1938 by a group of researchers working with an extract of lobster. The molecular structure of astaxanthin is presented in **Figure 1**.

Function

Astaxanthin is unique in sense that it does not only scavenge free radicals but also protect against oxidation and limit the production of free radicals. On the basis of reported studies, astaxanthin also increases the function of other antioxidants like Vitamin E and C [36]. Astaxanthin has been related to offer protection against the effects of ultraviolet (UV) light exposure [37]. There are limited evidences showing efficiency of astaxanthin in immune system, prevent skin ulcer due to various factors, reducing the amount of oxidized low density lipoprotein (LDL)-cholesterol and minimizing inflammation-induced cardiovascular disorder [38-40]. Astaxanthin has capacity to cross the blood brain barrier and scavenge free radicals in the brain and thus providing neuro-protection [41]. Anti-inflammatory activity paralleled with anti-oxidant properties. There are studies showing anti-inflammatory activity of astaxanthin [42-45]. Anti-inflammatory activity associated with limiting activity of nitric oxide

Table 1. Sources, function, and effects of different functional foods in cancer prevention

Functional foods	Dietary Sources	Function	Effects	References
α-Carotene	Yellow-orange and dark-green vegetables	Antioxidant	In moderate dose increase enhance gap junctional intercellular communication	[22]
β-Carotene	Green leafy vegetables and orange and yellow fruits and vegetables	Antioxidant	Similar α-Carotene	[22]
Lycopene	Tomatoes, water melon, apricot, peaches	Antioxidant	Lycopene is more potent than α and ß-carotene in inhibiting the cell growth of various human cancer cell lines	[23]
Lutein	Dark green leafy vegetables	Antioxidant	Lutein is efficient in cell cycle progression and inhibit growth of a number of cancer cell types	[24]
β-Cryptoxanthin	Orange fruits	Antioxidant	Anti-inflammatory effects; inhibits risks of some cancer	[25]
Astaxanthin	Green algae, salmon, trout	Antioxidant	The modification of gap junction communications	[26]
Canthaxanthin	Salmon, crustacea	Antioxidant	Free radical scavengers and potent quenchers of reactive oxygen species	[25]
Fucoxanthin	Brown algae, heterokonts	Antioxidant	Anti-cancer and anti-inflammatory	[25]
Isothiocyanates	Broccoli, cauliflower, kale	Antibacterial	Lowering risk of lung, breast, liver, esophagus, stomach, small intestine and colon cancers	[27, 28]
Flavonoids	Synthesize in plants	Antioxidant	Efficient in prevention or treatment of many cancers	[29, 30]
Probiotics	Yoghurt and fermented foods	Anti-allergy	Alleviating symptoms of cancer	[31]
Phyto-estrogens (genistein and daidzein)	Soya and Phyto-estrogens Rich foods	Anti-cancer (breast and prostate)	Compete with endogenous estrogens for binding to estrogen receptor	[32]
Fiber	In most foods (vegetable and cereals and etc.)	Lowering cholesterol	Lowering colon and prostate cancer	[33]
Omega-3	Fish or fish oil	Lowering cholesterol	Lowering breast and prostate cancer	[34, 35]
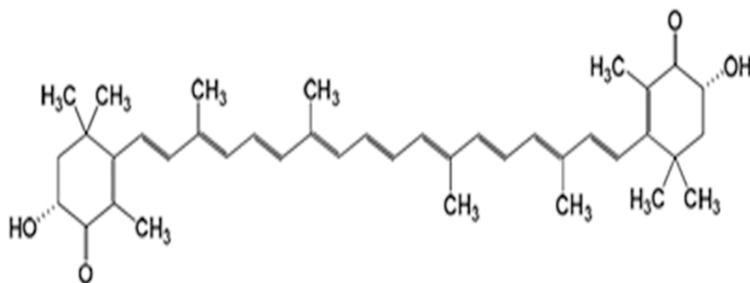
Figure 1. Molecular structure of astaxanthin.

synthase and the production of prostaglandin E2 and tumor necrosis factor-alpha (TNF-α) [42].

Anti-cancer activity

There are studies showing anti-cancer efficiency of astaxanthin [26, 46-48], although the mechanism of this association is not known. Some researchers believed the modification of gap junction communications is factor of anti-cancer activity [26, 47, 49], because of gap junction communications are key to homeostasis, growth control and development of cells. On basis of these studies, the gap junctional intercellular communication are faulted in cancer cells and astaxanthin influences channel functions by changing phosphorylation pattern of gap junction protein, connexion [26, 47]. Phosphorylation/dephosphorylation of functional connexion proteins in the membrane can affects channel gating and set channel action. In one review article by Tanaka et al. [25] showed astaxanthin contains two keto groups on each ring structure when compared with other carotenoids, resulting in powerful antioxidant properties. This claim that astaxanthin is super-antioxidant was confirmed by Pashkow et al. [50]. Additionally, of eight carotenoids tested, astaxanthin was the most effective at preventing the invasion of rat ascites hepatoma cells in culture [51]. On basis of these studies, astaxanthin have antioxidant activity, free radical scavengers, potent quenchers of reactive oxygen species and nitrogen oxygen species, and chain-breaking antioxidants [25]. Some other studies investigated effects of astaxanthin and canthaxanthin in *N*-butyl-*N* (4-hydroxy-butyl) nitrosamine (OH-BBN)-induced mouse urinary bladder carcinogenesis, [52] 4-NQO-induced rat oral carcinogenesis [53] and azoxy-

methane (AOM)-induced rat colon carcinogenesis [54]. The results of these studies showed the both specifically astaxanthin showed inhibitory role in association to cancer extension in urinary bladder [52], tongue [53] and colorectum [54] by the suppression of cell proliferation. As mentioned above that the inflammation is a cancer factor. In a study, it is reported that astaxanthin or lycopene inhibited proliferation of human prostate cancer [55]. Yasui et al. [56] demonstrated astaxanthin have the anti-inflammatory ability and anti-carcinogenesis in inflamed colon due to modulation of the expression of several inflammatory cytokines that are involved in inflammation-associated carcinogenesis. Seem, astaxanthin help to cyclooxygenase (COX)-2 down-regulations [57]. Another study suggested astaxanthin act by modulating nuclear factor kappa B (NF-κB), COX-2, matrix etalloproteinases (MMP) 2/9, extracellular signal-regulated kinase (ERK)-2 and protein kinase B (Akt) [58]. There is evidence showing that astaxanthin may inhibit the development of preneoplastic liver cell lesions induced by AFB1 in rats by the deviation of AFB1 metabolism towards detoxification pathways [59]. Also, tetrasodium diphosphate astaxanthin has been shown to completely prevent methylcholanthrene-induced neoplastic transformation of C3H/10T1/2 cells by up-regulation of connexin43 and gap junctional intercellular communication (GJIC) [60]. In addition in an animal study, astaxanthin prevented murine mammary tumor cell proliferation by 40%, in a dose-dependent fashion, when involved in the culture medium [61]. In other studies, dietary supplementing with astaxanthin prevented the growth of transplanted Meth-A tumor cells in a dose-dependent fashion in BALB/c mice's [62]. In another study, dietary intake of egg yolks containing astaxanthin prevented benzo (a) pyrene-induced mouse fore stomach neoplasia [63] and sarcoma-180 cell-induced mouse ascites cancer [64]. On the other hand; UVA radiation is primary causative agent in skin tumor pathogenesis. Lyons and O Brien [65] showed synthetic astaxanthin and astaxanthin-rich algal extract gave significant protection from UVA-
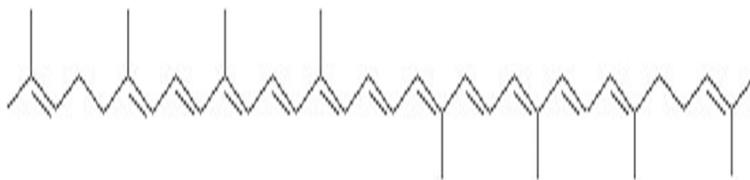
Figure 2. Molecular structure of lycopene.

induced DNA damage to human skin fibroblasts, melanocytes and intestinal CaCo-2 cells in culture. Also, dietary supplementing with astaxanthin inhibited the accumulation of potentially tumor-promoting polyamines in the skin of vitamin A-deficient hairless mice after exposure to UVA and UVB irradiation [66].

Lycopene

Structure

Lycopene is a 40 carbon atom, open chain hydrocarbon containing 11 conjugated and 2 non-conjugated double bonds assigned in a linear array (**Figure 2**). The tetraterpene-like structure is assembled from eight isoprene units. The bonds in the structure can undergo isomerization from the trans configuration to mono or polycis isomers via photo or chemical reactions. Due to the absence of P-ionone ring in the lycopene structure, it lacks provitamin-A activity [67]. The preponderance of conjugated double bonds in lycopene is believed to be responsible for its various protective effects, especially its singlet oxygen-quenching property and its ability to trap peroxyl radicals [68].

Function

Lycopene is a factor for the characteristic deep-red color of ripe tomato fruits and tomato products. Lycopene has biologic properties and profit effects in the therapy of different diseases [69]. Lycopene found in watermelon, grapefruit, apricots, pink guava, pawpaw, tomatoes and tomato based products account for more than 85% of lycopene in most diets [70]. Lycopene has multiple conjugated double bonds and it act as a powerful antioxidant and free radical quencher. Lycopene has been shown to have role in the decrease of cholesterol levels via the inhibition of cholesterol synthesis, elevation in low density lipoprotein degradation, and prevention of the hydroxyl-meth-

ylglutaryl-coenzyme A reductase enzyme [71]. Agarwal and Rao [67] documented that the singlet quenching ability of lycopene is twice as powerful as that of beta-carotene and 10 times higher than that of alpha-tocopherol. Earlier in this relation Fuhrman et al. [71] showed in six healthy male subjects given a dietary supplementating of 60 mg/day lycopene for 3 months, presented with a significant 14% decrease in plasma LDL cholesterol levels, although there were no observed impacts on HDL cholesterol contents. There are some other studies showing protective effects of lycopene consumption against risk of cardiovascular diseases, including atherosclerosis, myocardial infarction and stroke [72-74]. Also, anti-inflammatory activity of lycopene has been shown in both acute and chronic models of inflammation [75].

Anti-cancer activity

As mentioned before, the lycopene has antioxidant activity (singlet oxygen quenching and peroxyl radical scavenging), induction of cell-cell communication, and growth control, but it has no provitamin A action [68]. The many conjugated double bonds of lycopene make them potentially powerful antioxidants. Seem carotenoids (such as lycopene) may react with oxygen free radicals by either transfer of the unpaired electron leaving the carotenoid in an excited triplet state, the excess energy being dissipated as heat, or by 'bleaching' of the carotenoid. On the basis of these studies, lycopene is more potent than α and ß-carotene in preventing the cell growth of various human cancer cell lines [23]. In mouse models, lycopene has shown anti-carcinogenic roles in mammary gland, liver, skin and lungs, and also prevented the development of aberrant crypt foci in rat colon [76]. Lycopene in combination with α and β-carotenes (at a moderate dose) increased gap-junctional intercellular communication [22]. One study showed combination of lycopene and β-carotene reduced numbers and incidences of cancers [77]. There is an evidence showing S-allylcysteine from garlic and lycopene from tomatoes, in combination, this reduced the development of chemically induced gastric cancer by modulation of apoptosis-associated proteins (decreased Bcl-2/Bax ratio
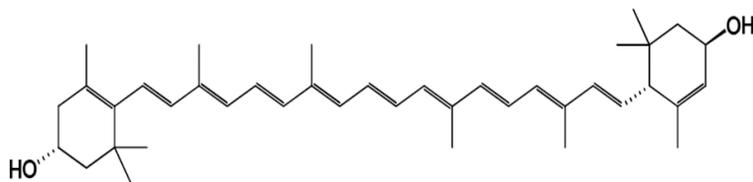
Figure 3. Molecular structure of lutein.

and up-regulation of Bim and caspases 8 and 3) at considerably lower intakes than when these substances were given in isolation [78]. Lycopene has been documented to prevent human cancer cell growth by interfering with the growth factors receptor signaling and cell cycle progression, specifically in prostate cancer cells, without known evidence of toxic impacts or cell apoptosis [79]. Sharoni et al. [80] showed that carotenoids and their oxidized derivatives interact with a network of transcription systems that are activated by different ligands at low affinity and specificity and that this activation leads to the synergistic prevention of cell growth. In one study, 30 mg/day of lycopene were given to 15 men, and 11 men other in the control group were recommended to follow the National Cancer Institute's recommendations to intake at least five servings of fruits and vegetables daily [81]. These findings cleared that lycopene slowed the growth of prostate cancer. Prostate tissue lycopene content was 47% more in the lycopene group. Subjects that took lycopene for 3 weeks had lower tumors, less involvement of the surgical margins and less diffuse involvement of the prostate by pre-cancerous high-grade prostatic intraepithelial neoplasia and prostate-specific antigen (PSA) levels had decreased by 17% [82]. There is a significant decrease in expression of connexins, including connexin43 in human tumors compared to normal tissue. Kucuk et al. [82] reported, an increase in level of connexin43, though not statistically significant, was observed among the prostate cancer patients supplemented with lycopene in the 3-week supplementation. As mentioned earlier that tomato contained lycopene. On the basis of these studies, lycopene prevents the mitogenic function of IGF-1 in human cancer cells. In mammary cancer cells, lycopene treatment markedly decreased insulin growth factor-1 (IGF-1) stimulation of both tyrosine phosphorylation of insulin receptor substrate-1 and the

DNA binding capacity of the activator 1 (AP-1) transcription role [83, 84]. These researchers also showed that the lycopene treatment of MCF-7 mammary cancer cells decreased IGF-1-stimulated cell cycle progression, which was not accompanied by either apoptotic or necrotic cell death. Lycopene-induced delay in development by the G1 and S phases has also been documented in other human cancer cell lines (leukemia and cancers of endometrium, lung and prostate) [85]. As mentioned earlier that the inflammation is an important factor for cancer. On the basis of these studies, lycopene prevents the production of the pro-inflammatory cytokine interleukin (IL)-8 induced by cigarette smoke. Yang et al. [86] showed that the anti-proliferative effect of lycopene on human prostate cancer cells (LNCaP) involves the activation of the PPARγ-LXRα-ATP-binding cassette transporter 1 (ABCA1) pathway. Lycopene had anticarcinogenic actions in mammary gland, liver, skin and lungs in mouse models, and also prevented the development of aberrant crypt foci in rat colon [76]. The inhibitory effect of tomato juice rich in lycopene (17 ppm) was observed in rat colon carcinogenesis model [87]. Long-term application (6 to 76 weeks of age) of a diet containing 0.005% lycopene did not decrease the risk of hepato-carcinogenesis in a rat spontaneous liver carcinogenesis model [88, 89]. Faezizadeh et al. [90] believed that lycopene may reduce cancer dangerous by K562 cells.

Lutein

Structure

The name lutein is derived from the Latin word for yellow (compare xanthophyll, vide supra). Lutein has the formula as $C_{40}H_{56}O_2$. Lutein belong to xanthophyll family. Lutein and zeaxanthin differ from other carotenoids is that they both of each have two hydroxyl groups, one on each side of the molecule. The molecular structure of lutein is presented in **Figure 3**.

Function

Lutein is especially concentrated in leafy green vegetables, many fruits, and colored vegeta-

bles such as sweet peppers, sweet corn, peas and egg yolk [91]. Maize was the vegetable with the highest quantity of lutein (60% of total) and also present in kiwi fruit, grapes, spinach, orange juice, zucchini (or vegetable marrow), and different kinds of squash [91]. Lutein is very good antioxidants in lens. On the basis of these studies, antioxidants can oppose cell damage and even the development of certain cancers by neutralizing free radicals [92]. There are studies documenting that lutein is more effective in inhibiting lipid peroxidation, and are themselves better protected against secondary oxidative breakdown when melatonin, glutathione, alpha-tocopherol and ascorbate are present [93]. Further epidemiological study on lutein associated that subject with the highest serum lutein had a significantly decreased risk of coronary heart disease (CHD), and a significant inverse relationship between lutein intake and the risk of stroke [94, 95]. The consumption of lutein and zeaxanthin was documented to supply protection against skin swelling (edema) and hyperplasia caused by UV exposure of the skin [96].

Anti-cancer activity

Lutein and zeaxanthin have been shown to reduce the risk of breast cancer by 53% [97]. As mentioned before, lutein is an antioxidant and similar other antioxidants functional foods act against cancer. Lutein quenches peroxy radicals and show antioxidant features against oxidative damage in vitro [98, 99]. Plasma lutein analyzed from 37 women associated inversely with assessed oxidative indices [100]. The strongest synergistic impact was gained in the presence of lutein or lycopene [101]. Lutein can be acting like anticarcinogenic as well. Lutein is capable to interact with the mutagens 1-nitropyrene and aflatoxin B1 (AFB1) [102, 103] or it may also exert an anticarcinogenic impact by stimulating certain genes involved in T-cell transformations activated by mitogens, cytokines and antigens [104]. The *Pim-1* gene involve in regulating cell differentiation and apoptosis. On the basis of these studies *pim-1* gene expression was stimulated in lutein-fed mice's [104, 105]. Narisawa et al. [106] indicated the protective impacts of lutein on preneoplastic colorectal adenocarcinoma lesions. In a study in Fijians, researchers showed an inverse relation between lutein and lung cancer

(Fijians consume an average of 200 g of dark green vegetables 25 mg lutein) daily [107]. Slattery et al. [108] showed an inverse relation between dietary lutein consumption and colon cancer in men and women. The decrease in risk was significant only in patients who were diagnosed with colon cancer at a younger age [108]. On the basis of these studies, low levels of dietary lutein at 0.002 and 0.02% of the diet prevented mammary tumor incidence, growth and latency [109]. Lutein has been indicated to induce apoptosis in transformed but not in normal human mammary cells, and to protect normal cells from apoptosis induced in cell culture [110]. Freudenheim et al. [97] have documented that the consumption of carotenoid-rich foods, specifically vegetables, as well as lutein, is significantly related with a lower risk of developing premenopausal breast cancer. In a case-control study, elevating serum levels of lutein were correlated with a lowered breast cancer risk, but the trend was only marginally significant [111, 112]. A reduced risk of cancer was correlated with increasing levels of breast adipose tissue lutein contents in women with breast cancer when compared with women with benign breast biopsies, but the relation was not significant [113]. In another study, consumption of lutein and zeaxanthin in the highest quintile (9 mg/day) had a significant 21% reduction in breast cancer risk relative to those in the lowest quintile (2 mg/day) [114]. In a similar other study, Gunasekera et al. [115] concluded lycopene, lutein, or their combination differentially prevent growth of a highly malignant line of prostate tumor cells (AT3) while exerting no impact on growth of the benign tumor parental cell line (DTE). This inhibitory impact is content dependent and does not represent a general cytotoxic response. As mentioned lutein is efficient in protective against skin damage, but unfortunately we cannot find any study showing chemo-protective effects lutein in skin cancer. Chethan Kumar and Veerabasappa Gowda [116] reported lutein at 20 µg/ml effectively prevented peroxidation of lipids, hydroxyl radical production and 1, 1-diphenyl-2-picrylhydrazyl (DPPH) radical production to the tune of 86%, 92% and 90% respectively, while, α-tocopherol, curcumin and butylated hydroxy anisole, when applied at dose ~12 times more (400 µM) than lutein indicted 75-95% inhi-
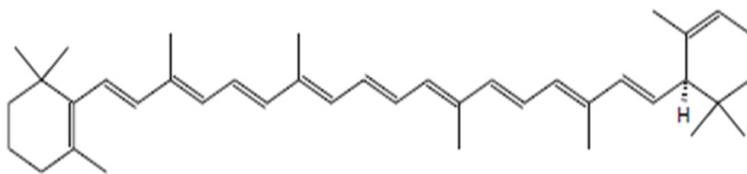
Figure 4. Molecular structure of α-carotene.
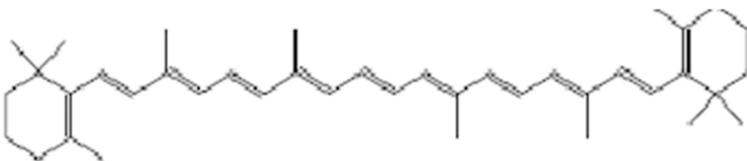
Figure 5. Molecular structure of β-carotene.

bition of lipid peroxidation and scavenging of hydroxyl and DPPH radicals. On the basis of earlier studies, low levels (0.002 and 0.02%) of dietary lutein reduced mammary tumor incidence, tumor growth and lipid peroxidation, and elevated tumor latency, while higher dietary levels (0.2 or 0.4%) were lower effective [117].

α-carotene

Structure

The α-carotene is cleaved symmetrically at their central double bond by β-carotene 15, 15'-monooxygenase (CMO1), formerly called β-carotene 15, 15'-dioxygenase. An alternative excentric cleavage pathway was also showed [188, 119] and confirmed by molecular identification of an excentric cleavage enzyme, β-carotene 9', 10'-monooxygenase (CMO2) in mice, humans, and zebrafish [120]. The molecular structure of α-carotene is presented in **Figure 4**.

Function

The richest source of α-carotene is carrots and carrot juice, with pumpkins and winter squash as a second densest source. There is approximately 1 µg of α-carotene for every 2 µg of β-carotene in carrots. Carotenoids are transported in the plasma by lipoproteins. The α-carotene tends to predominate in low-density lipoproteins (LDL) [121, 122]. The α-carotene has been shown to be a stronger protective factor than its well-known isomer β-carotene [123]. In a study, Narisawa et al. [106] indicat-

ed the protective effects of α-carotene on preneoplastic colorectal adenocarcinoma lesions.

Anti-cancer activity

Animal studies have shown that the α-carotene has higher activity than β-carotene in inhibiting tumorigenesis in the skin, lungs, liver and colorectum [106, 124]. In a skin tumorigenesis study done by Murakoshi et al. [124], the incidence of tumor-bearing mice in the positive control group was 69%, whereas those in the groups treated with α-carotene was by 25%. The average multiplicity (number of tumors/mouse) of tumors in the positive control group was 3.73/mouse, while the α-carotene-treated group had 0.13/mouse. In the same study, lungs carcinogenesis model initiated by 4-nitroquinoline 1-oxide (4-NQO) and promoted by glycerol, the average multiplicity of lungs tumors per mouse in the positive control group was 4.06/mouse, whereas the α-carotene-treated group had 1.33/mouse.

β-carotene

Structure

As mentioned β-carotene similar to α-carotene is cleaved symmetrically at their central double bond by β-carotene 15, 15'-monooxygenase (CMO1), formerly called β-carotene 15, 15'-dioxygenase. An alternative excentric cleavage pathway was also showed [118, 119] and confirmed by molecular identification of an excentric cleavage enzyme, β-carotene 9', 10'-monooxygenase (CMO2) in mice, humans, and zebrafish [120]. The molecular structure of α-carotene is presented in **Figure 5**.

Function

The β-carotene found in green leafy vegetables, orange, yellow fruits and vegetables. β-carotene can be converted to vitamin A in humans. β-Carotene and its oxidative metabolite, apo-14'-carotenoic acid, are shown to invert the down-regulation of RARβ by smoke-borne car-
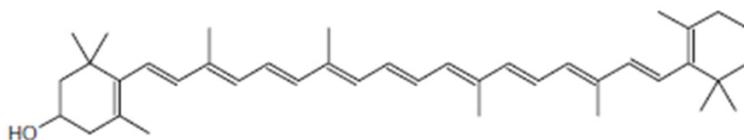
Figure 6. Molecular structure of β-Cryptoxanthin.

cinogens in normal bronchial epithelial cells [125]. Also, the transactivation of the RARβ enhancer through β-apo-14'-carotenoic acid shows to occur by its metabolism to all-*trans*-retinoic acid [125]. Thus, the molecular mode of the role of β-carotene may be mediated by retinoic acid by transcriptional activation of a series of genes with distinct anti-proliferative or pro-apoptotic activity, which access for the deletion of neoplastic and preneoplastic cells with irreparable alterations. The β-carotene prevented AFB1-induced preneoplastic hepatocellular lesions in rats [59]. The β-carotene was also shown to cause a cell-cycle delay in the G1 phase in normal human fibroblasts [126].

Anti-cancer activity

As mentioned before β-carotene act as an antioxidant, but it shows prooxidant impacts at high content and especially at high oxygen tension [127, 128] prooxidant impacts may help to explain the unexpected elevation in lung cancer deaths among smokers treated with β-carotene [128, 129]. β-carotene in combination with lutein quench peroxy radicals and show antioxidant features against oxidative damage *in vitro* [98, 99]. There are studies showing anticancer activity of β-carotene [23, 46, 109, 124]. In a study Toniolo et al. [130] documented an inverse relation between breast cancer and the serum concentration of β-Carotene. Similar findings reported in USA, China, Turkey, and India [131-133]. In a skin tumorigenesis study done by Murakoshi et al. [124], the incidence of tumor-bearing mice in the positive control group was 69%, whereas those in the groups treated with α-carotene was by 13%. In another study, β-carotene in combination with vitamin E and selenium reduced cancer dangerous by 13% and for stomach cancer by 21% [134]. Although there are some studies showing diet supplementing with β-carotene or vitamin A and vitamin E in smokers caused a significant increase in lungs cancer [135-137]. An increase in lungs cancer in smokers may be a result of imbalance of other carotenoids or antioxidants, a pro-oxidant function of β-carotene at the high oxygen tensions found in the lungs, induction of P450 enzymes and the production of damaging β-carotene oxidation products by components of cigarette smoke [138]. In another study, Rautalahti et al. [139] showed diet supplementing with β-carotene and α-tocopherol had no significant impact on rate of incidence of pancreatic carcinoma or the rate of mortality caused by this disease. Jayappriyan et al. [140] explained the β-carotene obtained from D. s*alina* microalga has anti-cancer activity.

β-cryptoxanthin

Structure

The β-cryptoxanthin is hydrocarbon carotenoid that is cyclized. The molecular structure of α-carotene is presented in **Figure 6**.

Function

Human milk contains cryptoxanthin that have varying degree of biologic activity. Whole wheat flour, the bran/germ fraction contributed of total β-cryptoxanthin [141]. The β-cryptoxanthin has found in oranges and orange juice, peaches, papayas, mangoes, watermelon, nectarines, fruit cocktail, plums, grapefruit, and black olives. Also, β-cryptoxanthin is abundant in red bell peppers, papayas and tangerines [142, 143]. It is precursors for vitamin A and it converted to retinol in the body [144]. There is one study documenting the effects of β-Cryptoxanthin on bone calcification through increasing alkaline phosphatase function and calcium concentration in rat femoral tissue and directly stimulating bone formation and preventing bone resorption [145]. There are several studies showing reverse correlation between β-cryptoxanthin contents and disease morbidity such as liver disorders [146, 147].

Anti-cancer activity

The β-cryptoxanthin acts in several biological activities, such as scavenging of free radicals, increase of gap junctions, immunomodulation and regulation of the enzyme activity involved
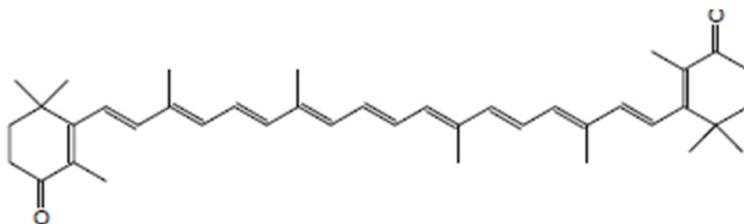
Figure 7. Molecular structure of canthaxanthin.

in carcinogenesis [148, 149]. In a study, Narisawa et al. [150] showed administration of 25 ppm of β-cryptoxanthin for 30 weeks in the diet significantly prevented N-methylnitrosourea-induced colon carcinogenesis in rats. In animal studies, *Citrus unshiu* segment membrane (CUSM) containing β-cryptoxanthin and fiber prevents colitis and obesity-related colon tumorigenesis [149, 151]. Serum levels of β-cryptoxanthin have been inversely associated with the occurrence of human cervical cancer [152]. In addition, the dietary consumption of β-cryptoxanthin is correlated with decreased risk for lung cancer [153]. In another study, Toniolo et al. [130] reported an increase in breast cancer in peoples receiving lower levels of β-cryptoxanthin. In addition, there are other reports documenting the efficiency of β-cryptoxanthin in preventing skin tumor formation in mice [76, 154].

Canthaxanthin

Structure

Canthaxanthin is hydrocarbon carotenoid that is cyclized. The molecular structure of canthaxanthin is presented in **Figure 7**.

Function

Canthaxanthin for first time was isolated from the edible mushroom, *Cantharellus cinnabarinus*. Also, it is found at the end of the growth phase in several green algae, blue-green algae, or in addition to, primary carotenoids. It has in bacteria, crustacea and various species of fish including carp (*Cyprinus carpio*), golden mullet (*Mugil auratus*), annular seabream (*Diplodus annularis*) and trush wrasse (*Crenilabrus tinca*) [25]. Canthaxanthin is also not generally considered a dietary carotenoid, but it may be included in the human diet by its widespread application as a coloring factor in foods and

animal feeds [144, 155]. In addition, Canthaxanthin has an antioxidant action, are free radical quenchers, potent quenchers of reactive oxygen species (ROS) and nitrogen oxygen species, and chain-breaking antioxidants. Canthaxanthin is a superior antioxidant and scavengers of free radicals when compared with the carotenoids such as β-carotene [50]. Canthaxanthin is one of the carotenoids without provitamin activity [25]. Canthaxanthin is documented to be able to suppress the development of preneoplastic liver cell lesions caused by AFB1 in rats by the deviation of AFB1 metabolism towards detoxification pathways [59].

Anti-cancer activity

The Canthaxanthin may prevents proliferation of human colon cancer cells protect mouse embryo fibroblasts from transformation [156] and kept mice from mammary and skin tumor development [157]. Canthaxanthin has also proved effective at preventing both oral and colon carcinogenesis in rats [53, 54]. Although it is a potent antioxidant, the chemopreventive impacts of canthaxanthin may also be associated to its ability to up-regulate gene expression, resulting in increased gap junctional cell-cell communication [158, 159]. There are evidences showing that the canthaxanthin is pure antioxidants because it shows little or no pro-oxidative behavior even at high carotenoid content and high oxygen tension [160, 161]. The chemopreventive effects of canthaxanthin may also be correlated to its ability to induce xenobiotic metabolizing enzymes, as has been shown in the liver, lungs and kidneys of rats [162, 163]. Canthaxanthin overuse as a sunless tanning product has caused to the appearance of crystalline deposits in the human retina [164]. There are some other studies showing induction of some enzymes by canthaxanthin. The group of researchers showed canthaxanthin included P4501A1 and 1A2, and CYP1A1 and 1A2, which are involved in the metabolism of such potential carcinogens as polycyclic aromatic hydrocarbons, aromatic amines and aflatoxin [59, 162, 165]. This xanthophyll also induced selected P450 enzymes in rat lung and kidney tissues, but not in the small intestine
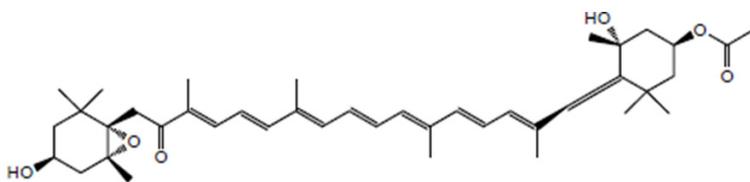
Figure 8. Molecular structure of fucoxanthin.

[163]. Although these retinal administrations are reversible [166] and show to have no adverse effects [164] their existence has enhanced caution regarding consumption of this carotenoid. On the basis of these studies, canthaxanthin shows inhibitory effects on cancer development in urinary bladder [52], tongue [53] and colorectum [54] by the prevention of cell proliferation. Canthaxanthin has also showed cancer chemopreventive actions in UV-B-induced mouse skin tumorigenesis [167] and chemically-induced gastric [168] and breast carcinogenesis [168, 169]. Canthaxanthin may inhibit the proliferation of human colon cancer cells and kept mouse embryo fibroblasts from transformation [156] and mice from mammary and skin tumor development [157]. Canthaxanthin is efficient in preventing both oral and colon carcinogenesis in rats [53, 54].

Fucoxanthin

Structure

Fucoxanthin is hydrocarbon carotenoid that is cyclized. The molecular structure of fucoxanthin is presented in **Figure 8**.

Function

The Fucoxanthin is a naturally occurring brown or orange-colored pigment that exist in the class of non-provitamin A carotenoids. Fucoxanthin involved as an antioxidant under anoxic conditions [25]. Fucoxanthin is found in *Chromophyta* (*Heterokontophyta* or *Ochrophyta*), including brown seaweeds (*Phaeophyceae*) and diatoms (*Bacillariophyta*) [170]. There is a study showing fucoxanthin influences multiple enzymes involved in fat metabolism causing an elevating in the production of energy from fat [171]. Fucoxanthin may be capable for an increase in circulating cholesterol levels in rodents as a common feature [170].

Anti-cancer activity

On the basis of *in vitro* studies the fucoxanthin is capable in preventing of cell lines developed in liver (HepG2) [172], colon (Caco-2, HT-29 and DLD-1) [173] and urinary bladder [174]. Also, it shows some inhibitory effect in induction of apoptosis [173, 174] and the preventing of cyclin D levels [172] that these are necessarily for the growth of cancer cells. In a study, Kim et al. [175] showed fucoxanthin inhibit DMH-induced mouse colon carcinogenesis. Also, it may inhibits spontaneous liver tumorigenesis in C3H/He male mice and showed antitumor-promoting activity in a two-stage carcinogenesis experiment involving the skin of ICR mice, initiated with 7,12-dimethylbenz[*a*] anthracene and increased with 12-*O*-teradecanoylphorbol-13-acetate and mezerein [176]. Also, fucoxanthin has been shown to prevent duodenal carcinogenesis induced by *N*-ethyl-N'-nitro-*N*-nitrosoguanidine in mice [177]. It's believed anticancer activity of fucoxanthin associated to biomolecules involving in cell cycle and apoptosis [178, 179] and those related with antioxidant activity by its pro-oxidant role [180]. There is another study showing fucoxanthin is able to selectively prevent mammalian DNA polymerase activities, especially replicative DNA polymerases (*i.e.*, pol α, δ and ε), and thus has anti-neoplastic role [181]. Fucoxanthin may change cell cycle progression [182]. In one research article Hosokawa et al. [173] has been shown fucoxanthin can induce apoptosis and increase the anti-proliferative impacts of the PPARγ ligand, troglitazone, and prevent the growth of human colon cancer cells. Fucoxanthin has the ability to care against oxidative stress caused by UV-B radiation and which may be applied to antioxidant and cosmeceutical industries. Sangeetha et al. [183] showed that fucoxanthin has greater potential than beta-carotene in modulating lipid peroxidation, catalase and glutathione transferase in plasma and liver of retinol deficiency rats. Fucoxanthin inhibits skin photoaging in UVB-irradiated hairless mice, possibly by antioxidant and antiangiogenic impacts on topical treatment [184]. Fucoxanthin prevented tyrosinase function, melanogenesis in melanoma and UVB-induced skin pigmentation [185]. Fucoxanthin-induced
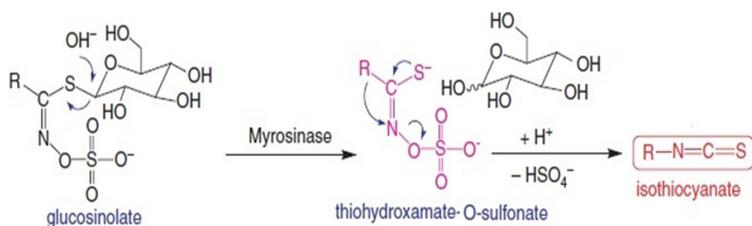
Figure 9. Molecular structure of isothiocyanate.

apoptosis in human leukemia cell HL-60 cells triggered Bcl-xL signaling pathway in HL-60 cells. On the basis these studies fucoxanthin prevented the growth of LNCap prostate cancer cells in a dose-dependent manner. Fucoxanthin activated c-Jun N-terminal kinase (SAPK/JNK), while the prevention of SAPK/JNK attenuated the induction of G (1) arrest and GADD45A expression by fucoxanthin [186]. Fucoxanthin treatments were found to cause apoptosis by caspase-3 activation in PC-3 human prostate cancer cells [187].

Isothiocyanates

Structure

Isothiocyanates are a group of phytochemicals containing sulphur that occur naturally as glucosinolates conjugated. It has been shown in **Figure 9**, enzyme myrosinase present in plant tissues or intestinal flora catalyzes the breakdown of glucosinolates such as glucoraphanin to isothiocyanate sulforaphane.

Function

The Isothiocyanates is found in cruciferous vegetables such as broccoli, cauliflower, kale, Brussels sprouts, cabbage, and others. Glucosinolates found in high amount in cruciferous vegetables [188] but unfortunately its bioavailability is highly affected by food processing operations such as boiling or microwaving in high power [189]. Isothiocyanates existed in form sulforaphane in broccoli (sprouts) and phenethylisothiocyanate in watercress.

Anti-cancer activity

Several studies have documented that isothiocyanates and their metabolites assist to lower the risk of developing different types of cancer such as lungs, breast, liver, esophagus, stomach, small intestine and colon [27, 28]. It's believed that the isothiocyanates act through modulation in cytoprotective biotransformation enzymes by the Kelch-like erythroid-cell-obtained protein with CNC homology (ECH)-related protein 1 (KEAP1)/Nuclear factor erythroid 2-related factor 2 (NRFF2)/antioxidant response element (ARE) pathway, anti-inflammatory activity by prevention of nuclear factor kappa B (NFκB), prevention of proliferation by induction of cell cycle arrest and programmed cell death (apoptosis), induction of hormone receptor expression, antiangiogenic and antimetastasis potential, and induction of autophagy [190, 191]. There is an evidence showing association between immunoprecipitation and sulforaphanes, so that chromatin-immunoprecipitation using an antibody against the transcription factor nuclear factor erythroid 2-related factor 2 coupled with sequencing of the chromatin-bound DNA (ChIP-seq) has recently revealed more than 240 genomic regions bound to nuclear factor erythroid 2-related factor 2 after stimulation of human lymphoblastoid cells with sulforaphanes [192]. NRF2 stimulates anti-stress signaling with protective response to suppress oxidative or electrophilic stress and prevents carcinogenesis [193]. In the resting state NRF2 is inactive due to proteasomal degradation produced by a negative regulator KEAP1 (Kelch-like ECH associated protein 1). In addition, Wagner et al. [194] showed sulforaphane and allylisothiocyanate lowered lipopolysaccharide-induced NF-κB-mediated transcription of proinflammatory proteins in murine macrophages. On the basis of *In vitro* studies, the time- and dose-dependent responses with sulforaphane induced phase II enzymes. The action demonstrating the positive impact of enzymatic activities of GST, NAD(P)H: quinone oxidoreductase 1 (NQO1), aldo-keto reductase (AKR) and glutathione reductase (GR) in several mammalian cancer cell lines: HepG2, MCF7, MDA-MB-231, LNCaP, HeLa and HT-29 [195]. Seem sulforaphane act in prevention of cancer by histone deacetylases (HDACs) [196] documenting its chemopreventive activities to post-initiation stages. It's documented, HDAC inhibitors may

cause growth arrest, apoptosis, reactive oxygen species facilitated cell death and mitotic cell death in cancer models [197]. In confirmation of this idea, Seligson et al. [198] showed a decline in the histone acetylation state correlates with elevated grade of cancer and risk of prostate cancer recurrence. On the basis of these studies, sulforaphane at concentration of 75 µM may cause G1/G2 cell cycle arrest and induce apoptosis through down regulating anti-apoptotic bcl-2 expression and elevating apoptosis-causing bax expression in colon cancer Caco-2 cells [199, 200]. It was documented that sulforaphane can more effectively prevent the growth of MCF-7 human breast cancer cells when compared with MCF-12A normal human breast epithelial cells (IC50 40.5 µM) for 48 h treatment [201]. It's well known that *Helicobacter pylori* associated with increase in the risk of developing gastric cancer [202]. On the basis of these studies, sulforaphane was shown to kill or prevent the growth of multiple strains [203], and it is leading in some cases to eradication [204]. Isothiocyanates all have been shown to induce apoptosis in cancer cells preferentially over normal cells [205]. In one interested work, Mi et al. [206] treated human lungs cancer cells by radioactivity-labelled ^{14}C-sulforaphane and ^{14}C-phenethylisothiocyanate. On the basis of older studies, administration of the phenyl ethyl isothiocyanate 7, 12-dimethylbenz[a] anthracene caused an inhibition in mammary carcinogenesis in rats [207]. In an animal study, administration of 10 µmol sulforaphane in *APC* mice's (mouse model of multiple intestinal neoplasia with *APC* gene mutation), prevented HDAC activity in the colonic mucosa and suppressed tumor development [208]. Interestingly, combination of green tea polyphenols and sulforaphane significantly lowered cellular proliferation, likely by the pronounced impact of histone modifications as well as DNA demethylation-mediated ERα activation in MDA-MB-231 cells [209]. In another study, diet supplementing by broccoli sprouts or two percent broccoli sprout isothiocyanate extract, or gavage of pure sulforaphane resulted in tumor weight reduction by 42%, 33% and 58%, respectively in murine UMUC3 invasive bladder cell xenograft model [210]. In an additional other study, sulforaphane prevents the growth of the epithelial ovarian cancer cell (EOC) line SkOV-3 by down-regulating AKT activity [211]. There is an evidence documenting the efficacy of sulforaphane against human brain malignant glioma GBM 8401 cells [212] and human lungs adenocarcinoma LTEP-A2 cells with growth prevention belong to *in vivo* models [213].

Probiotic, prebiotic and symbiotic

Structure

There are many definitions for probiotics. In most researches, probiotic defined as living microorganisms which when ingested in certain amounts, they have positive effects on human health, by improvement of the balance of the intestinal microflora [214]. Prebiotics are non-digestible food compositions that may have positive impact by the improvement of the intestinal flora. Synbiotics are combination of the both (pre and probiotic) and they contained beneficial bacteria that prompt benefit bacterial growth.

Function

On the basis of several studies of different strains, species and genera of bacteria have positive effects on inflammatory bowel disease [215, 216] lactose intolerance [217, 218] reduce in hypertension [219, 220] inhibit in growth of *Helicobacter pylori* [221, 222] and lowering cholesterol [223, 224]. Prebiotics may have effects of antimicrobial, anticarcinogenic, hypolipidemic, glucosemodulatory and anti-osteoporotic activities. Synbiotics may have positive effects on benefit bacterial growth and health in general.

Anti-cancer activity

There are quite a good works documenting the efficiency of probiotics in prevention of cancer growth cancer [123, 219, 225]. Some strains of bacteria such as (*L. acidophilus and B. longum*) have been documented for its protective effects in cancer pathogenesis [226]. Probiotics inhibit putrefactive intestinal bacteria with deleterious enzymatic function which generate carcinogenic substances from dietary components and change procarcinogens into carcinogens [227]. Probiotics have indicated species and dose-dependent protective impacts against DNA damage caused by colon carcinogens including N-methyl-N-nitro-N-nitrosoguanidine (MNNG) and DMH [228].

Seem a combination of pro and prebiotics (synbiotics) have positive impacts on prevention of cancer pathogenesis. In a study, synbiotics improved composition of colonic bacterial ecosystem, reduced exposure of the epithelium to cytotoxins and genotoxins, and improved mucosa structure [227]. This mechanism may help to decrease in colorectal cancer. Burns and Rowland [229] showed an increase in lactobacillus population caused a decrease in bacterial enzymes that is active for carcinogens, tumor promotion. In relation with metabolizing enzymes, Wollowski et al. [228] showed strains such as *Bacteroides, Clostridium,* and *Enterobacteriaceae* produce xenobiotic-metabolizing enzymes as NADPH dehydrogenase (azoreductase), nitroreductase, and b-glucuronidase. In this relation Burns and Rowland [229] in rats showed change in enzyme function and metabolite content lowered preneoplastic lesions such as aberrant crypt foci (ACF) and tumors in carcinogen-treated. Accordingly administration of *B. longum* (4 × 10^8 viable cells/g diet) reduced small ACF caused by colon carcinogen (azoxymethane) in rats by 26% [230]. It's well-known that born foods produced heterocyclic amines and polycyclic aromatic hydrocarbons that they are carcinogen factor. In a study on rats Challa et al. [231] showed administration of *B. longum* and lactulose caused an increase in activity of glutathione transferase enzymes (inactivating enzyme of polycyclic aromatic hydrocarbons). On the basis of one research article, administration of extracellular extract of a commercial probiotic (*Bacillus polyfermenticus*) prevented growth of human colon cancer cells such as HT-29, DLD-1 and Caco-2 cells, decreased carcinogen-induced colony production of normal colonocytes, and lowered tumor size in mouse xenograft model of human colon cancer cells [232]. It's believed probiotics may act through the production of conjugated linoleic acid. In animals' models, conditioned medium containing probiotic-produced conjugated linoleic acid decreased viability and caused apoptosis of HT-29 and Caco-2 colon cancer cells [226].

Phyto-estrogens (genistein and daidzein)

Structure

Phytoestrogens are classified into three main categories: isoflavones (genistein, daidzein, gly-

citein or equol), lignans (enterolactone or enterodiol) and coumestans (coumestrol).

Function

On the basis of reported studies, the phytoestrogens act similar to estrogens. They may act in the body either with estrogenic or anti-estrogenic impacts [233]. There are studies documenting positive role of phytoestrogens in the skeleton and the cardiovascular system [234], decrease the frequency of osteoporosis [235] and attenuate menopausal symptoms [236].

Anti-cancer activity

Flavonoids (genistein), stilbenes (resveratrol), polyphenols (curcumin), and isothiocyanates all have been shown to causing apoptosis in cancer cells preferentially over normal cells [205]. (Phytoestrogens may inhibit breast cancer [237], prostate cancer [238] endometrial cancer, thyroid cancer [239], skin cancer [240] and colorectal cancer [241]. In an examination, combination of vitamin D3 with genistein prevented of growth of prostate cancer cells at much lower concentrations compared with single form [242]. The mechanism for the association may associate to presence of genistein in combination with vitamin D, because genistein prevents cytochrome P-450 isoenzyme CYP24 expression and activity. Partly similar to previous study, the combination of quercetin and genistein synergistically prevent growth of ovarian carcinoma cells by modifying different stages in the cell cycle and different signal transduction pathways [242]. Yeh et al. [243] concluded that genistein is an efficient isoflavonoid that causes apoptotic signaling in a sequential manner in Hep3B cells. It creates endoplasmic reticulum stress, which is characterized through the elevation of calcium mobilization, cleavage of m-calpain, up-regulation of GRP78 and GADD153 expression, and activation of caspase-12. Genistein also creates the activation of executor caspase-3 and caspase-7. In addition, the interaction with mitochondrial stress to down-regulate Mcl-1 level and to produce truncated Bad may facilitate genistein-mediated apoptosis in Hep3B cells. On the basis of these evidences, genistein and daidzein may play a main function in reducing cancer risk come from epidemiologic investigations because populations with high isoflavones exposure by soy intake have low cancer

rates [244, 245]. The new detection of a new estrogen receptor b (ERb), particularly present in the brain, heart, bones, and urogenital system and binds phytoestrogens with relatively high affinity [246] has further elevated interest in these compounds.

Fiber

Structure

Dietary fibers classified into soluble or insoluble. More recently, some are proposing the use of the terms "viscous" and "fermentability" in place of soluble and insoluble to describe the functions and health advantageous of dietary fiber.

Function

The intake of dietary and functional fibers has many potential health advantageous, namely the ability to reduce the frequency of constipation [247] and irritable bowel syndrome [248] reducing cholesterol and diminish the frequency of coronary and cardiovascular heart diseases [249] inhibition obesity [250] and diabetes [251].

Anti-cancer activity

Some relatively recent studies showed reverse correlation between dietary fiber and the development of several types of cancers such as colorectal, small intestine, oral, larynx and breast [252-254]. In a research of Rafter et al. [227] showed that inulin reduced biological compounds related with colonic cancer, such as decreased colorectal cell proliferation and water caused necrosis, lowered exposure to genotoxins, and reduced interleukin-2 release. High fiber diet prevents prostate cancer progression in early stages based on Asian and Western cultures [255].

Omega 3

Structure

The omega-3 fatty acids are obtained from linolenic acid. The number following "omega-" shows the position of the first double bond, counting from the terminal methyl group on the molecule. There are three major types of omega-3 fatty acids including; alpha linolenic acid (ALA), which is the basic omega-3 fatty

acid, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA).

Function

Omega-3 fatty acids found in fatty fish with high oil content, consist of both eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Omega-3 fatty acids can also be found in some leafy vegetables, nuts, and oils as a-linolenic acid. Excessive amounts of omega-6 polyunsaturated fatty acids and a very high omega-6/omega-3 ratio, as is shown in today's Western diets, encourage the pathogenesis of many diseases, such as cardiovascular disease, cancer, and inflammatory and autoimmune diseases, while elevated levels of omega-3 PUFA (a lower omega-6/omega-3 ratio), exert inhibitory impacts. On the basis of another study, dietary supplementing with omega 3 had reverse correlation with cancer, inflammatory bowel disease, rheumatoid arthritis, and psoriasis [256].

Anti-cancer activity

On the basis of epidemiological studies, people who use diets high in omega-3 fatty acids may experience a lower prevalence of some types of cancer [257, 258] and some studies have tried to evaluate the impacts of omega-3 fatty acids on cancer treatment through omega-3 supplementing to the diet either as omega-3 fatty acid-rich foods or as dietary supplements [259, 260]. Gerber [261] reviewed prospective and case-control studies evaluating the possible protective impacts of the dietary consumption of omega-3 fatty acids on cancer development. In a relevant study in Hawaiian Island of Oahu, fish supplementing had reverse association with cell carcinoma of the oral cavity or pharynx, esophagus, or larynx [262]. Chyou et al. [263] showed fish intake had no significant impact on the bladder cancer.

Flavonoids

Structure

Flavonoids are large family of polyphenolics synthesized in plants. They can be classified into many different subclasses, each subclass divided to different compounds: anthocyanidins, chalcones, flavanols, flavones, flavanones, flavonols, flavononols, and isoflavones [264, 265].

Function

As mentioned before, flavonoids are large family of polyphenolics synthesized in plants. Flavonoids have positive effects for body including; antiviral [266] antitoxic, anti-fungal [267] antibacterial [268] anti-allergic [269] anti-inflammatory [270] and antioxidant activities [264]. On the basis of some other studies, flavonoids have positive effects in prevention of heart diseases [271].

Anti-cancer activity

There are studies showing, flavonoids have positive impact on the prevention and/or therapy of many different types of cancer such as: ovarian [272] colon [273] lungs [274] laryngeal [275] prostate [29], pancreatic [276] esophageal [277] breast [278] leukemia [30], renal cell carcinoma [279] and hepatocellular carcinoma [243], among others. On the basis of these studies phenolic flavonoids such as green tea polyphenols and epigallocatechin-3-gallate [280, 281] act as anticancer agents through activating transcription system. More evidences suggested that the anticancer effects of flavonoids related to various mechanisms, including the setting of cell cycle progression [282], prevention of kinase and protease activities [283, 284] stop of the secretion of matrix metalloproteinases [285] and prevention of the induction of activator protein-1 function [286]. The plant extracts prevent the synthesis of inflammatory mediators such as cyclooxygenase (COX)-2 mediated PGs, leukotrienes, and cytokines [287]. Also, certain products from plants are known to create apoptosis in malignant cells [288, 289]. In confirmation this claim, Hostanska et al. [274] showed bark extract BNO 1455 its fractions prevent the cell growth and promote apoptosis in human colon and lung cancer cell lines irrespective of their COX-selectivity. Also, apigenin (isoconformer of genistein) has shown more potent growth prevention in several cancer cell lines [290]. Apigenin has been documented to possess anti-inflammatory effects, free radical scavenging features, and anti-carcinogenic impacts [291]. It has been reported to possess growth inhibitory effects in several cancer lines, including breast, colon, skin, thyroid, and leukemia cells [292, 293]. In this association, Ujiki et al. [276] showed apigenin prevents growth of pancreatic cancer cells by suppression of cyclin B associated cdc2 activity and G2/M arrest, and may be a valuable drug for the therapy or inhibition of pancreatic cancer. Rossi et al. [277] reported flavanones consumption is reversely related with esophageal cancer risk and may account, with vitamin C, for the protective impact of fruit, especially citrus fruit, on esophageal cancer. In these relations, Fink et al. [278] documented that consumption of flavonols, flavones, flavan-3-ols, and lignans is related with lowered risk of incident postmenopausal breast cancer among Long Island women. Flavonoids have several important biological roles, which may be associated to cancer risk. In vitro and animal model systems indicated that they influence signal transduction pathways, stimulate apoptosis and prevent inflammation and proliferation in human cancer cell lines [294]. Selected flavonoids may also elevate transcription of phase II detoxifying enzymes, involved in the clearance of procarcinogenic substances [295]. Isoflavones prevent prostate cancer because isoflavones possess weak estrogen activity, prevent tyrosine protein kinases and angiogenesis, and decrease serum testosterone level [296, 297]. Isoflavones also prevent 5areductase, an enzyme that metabolizes testosterone to dihydrotestosterone [298]. Any or all of these mechanisms may attribute the reverse relations between isoflavones and localized prostate cancer. In addition, animal studies in rats showed that the beneficial impacts of a soy diet play a role in the early stages of tumor development but have no impact in invasive prostate cancer [299]. In relation with colorectal cancer and isoflavonoids, Theodoratou et al. [273] showed strong and linear reverse relations of flavonoids intake with colorectal cancer risk. However various compounds (fiber and folate) found in plant foods have protection effects against colorectal cancer. Other studies showed by 40% reduction in risk of colorectal cancer in peoples that consume fiber [300, 301] and by 30% reduction in individuals that consume folate [302]. Farmer et al. [303] reported the expansion of cancer care and control in countries of low and middle income: a call to action. This policy paper includes the need for implementation science research in low- and middle-income countries to guide effective cancer preventions and control in these settings. In another study Hunter and

Reddy [304] emphasize the need for global research efforts to inform the prevention, detection, and treatment of non-communicable diseases and outline the essential elements for effective cancer research, as well as priorities for implementation science to guide cancer control. Addressing the growing international challenge of cancer summarize the recommendations of this review, including priorities for research, of representatives of institutions and organizations that fund and perform cancer research. The WHO action provides guidance on public health priorities and thus key implementation science issues related to cancer prevention and control.

Conclusion

In general, this paper discusses nutraceutical/functional foods/food supplements (broadly including carotenoids fibers, probiotics, prebiotics, synbiotics, phytochemicals *etc.*), especially the need for consuming appropriate diets, health issues surrounding failure to adhere to the known healthy eating models, development of new nutraceutical/functional foods/food supplements with novel health benefits, elucidation mechanisms of action of these products, development of study systems such as *in-vitro* co-culture cell models. Vitamins and minerals are functional food and we hope to present that these reports in relation with effects of vitamins and minerals will help in designing food in future. An appropriate diet culminates in a healthy, properly functioning gastrointestinal tract, resulting in achievement of proper human physiology, hence healthy living; otherwise the pathology or opposite becomes true. One way that health systems expand intervention coverage is through selected platforms that deliver interventions that require similar logistics but deliver interventions from different packages of conceptually related interventions, for example, against cardiovascular disease with reference to functional foods. These types of platforms often provide a more natural unit for investment than do individual interventions. This comprehensive review is intended to spur that effort in populations lacking access to health insurance or prepaid care, medical expenses that are high relative to income can be impoverishing. Where incomes are low, seemingly inexpensive medical procedures can have catastrophic financial effects. Each individual will provide valuable, specific policy analyses on the full range of interventions, packages, and policies relevant to its health topic of functional food and cancers.

Acknowledgements

Disclosure of conflict of interest

None.

Address correspondence to: Nasroallah Moradi Kor, Young Researchers and Elite Club, Kerman Branch, Islamic Azad University, Kerman, Iran. Tel: 0098-9120734654; E-mail: Moradikor.nasroallah@yahoo.com

References

[1] Ames BN, Shigenaga MK, Hagen TM. Oxidants, antioxidants, and the degenerative diseases of aging. Proc Natl Acad Sci U S A 1993; 90: 7915-32.

[2] Abrams JS, Mooney MM, Zwiebel JA, Korn EL, Friedman SH, Finnigan SR, Schettino PR, Denicoff AM, Kruhm MG, Montello M, Misra RR, Ansher SS, DiPiazza KJ, Souhan EM, Wickerham DL, Giantonio BJ, O'Donnell RT, Sullivan DM, Soto NI, Fleming GF, Prindiville SA, Petryshyn RA, Hautala JA, Grad O, Zuckerman BL, Meyer RM, Yao JC, Baker LA, Buckner JC, Hortobagyi GN, Doroshow JH. Implementation of timeline reforms speeds initiation of national cancer institute-sponsored trials. J Natl Cancer Inst 2013; 105: 954-59.

[3] Arbyn M, Ronco G, Anttila A, Meijer CJ, Poljak M, Ogilvie G, Koliopoulos G, Naucler P, Sankaranarayanan R, Peto J. Evidence regarding human papillomavirus testing in secondary prevention of cervical cancer. Vaccine 2012; 30 Suppl 5: F88-99.

[4] Ames BN, Shigenaga MK. Oxidants are a major contributor to aging. Ann N Y Acad Sci 1992; 663: 85-93.

[5] Okada F. Inflammation and free radicals in tumor development and progression. Redox Rep 2002; 7: 357-66.

[6] Vel Szic KS, Palagani A, Hassannia B. Phytochemicals and cancer chemoprevention: epigenetic friends or foe? In: Rasooli I, editor. Phytochemicals-bioactivities and impact on health, InTech, Janeza Trdine 9, 51000 Rijeka, Croatia: 2011.

[7]   Bragg FL, Smith M, Guo Y, Chen Y, Millwood I, Bian Z, Walters R, Chen J, Yang L, Collins R, Peto R, Lu Y, Yu B, Xie X, Lei Y, Luo G, Chen Z; China Kadoorie Biobank Collaborative Group. Associations of blood glucose and prevalent diabetes with risk of cardiovascular disease in 500,000 adult Chinese: the China Kadoorie Biobank. Diabet Med 2014; 31: 540-51.

[8]   Tantamango-Bartley Y, Jaceldo-Siegl K, Fan J, Fraser G. Vegetarian diets and the incidence of cancer in a low-risk population. Cancer Epidemiol Biomarkers Prev 2013; 22: 286-94.

[9]   Chen Y, Li L, Zhang Q, Clarke R, Chen J, Guo Y, Bian Z, Pan X, Peto R, Tao R, Shi K, Collins R, Ma L, Sun H, Chen Z; China Kadoorie Biobank Study. Use of drug treatment for secondary prevention of cardiovascular diseases in urban and rural communities of China: China Kadoorie Biobank Study of 0.5 Million People. Int J Cardiol 2014; 172: 88-95.

[10]   Chen Z, Chen J, Collins R, Guo Y, Peto R, Wu F, Li L; China Kadoorie Biobank (CKB) collaborative group. China Kadoorie Biobank of 0.5 million people: survey methods, baseline characteristics and long-term follow-up. Int J Epidemiol 2011; 40: 1652-66.

[11]   Kuno T, Tsukamoto T, Hara A. Cancer chemoprevention through the induction of apoptosis by natural compounds. Biophys Chem 2012; 3: 156-73.

[12]   Shin JA, Kim JS, Hong IS, Cho SD. Bak is a key molecule in apoptosis induced by methanol extracts of Codonopsis lanceolata and Tricholoma matsutake in HSC-2 human oral cancer cells. Oncol Lett 2012; 4: 1379-83.

[13]   Wu QJ, Yang Y, Vogtmann E, Wang J, Han LH, Li HL, Xiang YB. Cruciferous vegetables intake and the risk of colorectal cancer: a meta-analysis of observational studies. Ann Oncol 2013; 24: 1079-87.

[14]   CSPI Reports. Public Health Boon or 21st Century Quackery? International, Functional Foods, Center for Science in the Public, 1998. Available online http://www.cspinet.org/reports/functional foods/introduction.html/.

[15]   Chen Z, Yang G, Offer A, Zhou M, Smith M, Peto R, Ge H, Yang L, Whitlock G. Body mass and mortality in China: a 15-year prospective study of 220,000 men. Int J Epidemiol 2012; 41: 472-81.

[16]   Food and Agriculture Organization of the United Nations (FAO). Report on Functional Foods, Food Quality and Standards Service (AGNS). Available online: http://www.fao.org/ag/agn/agns/files/Functional_Foods_Report_Nov2007. pdf.

[17]   Chiller JT and Lowy DR. Virus infection and human cancer: an overview. Recent Results Cancer Res 2014; 193: 1-10.

[18]   Sporn MB, Suh N. Chemoprevention: an essential approach to controlling cancer. Nat Rev Cancer 2002; 2: 537-543.

[19]   Lee BM, Park KK. Beneficial and adverse effects of chemopreventive agents. Mutat Res 2003; 23: 265-78.

[20]   De Martel C, Ferlay J, Franceschi S, Vignat J, Bray F. Global Burden of Cancers attributable to infections in 2008: a review and synthetic analysis. Lancet Oncol 2012; 13: 607-15.

[21]   Dikshit R, Gupta PC, Ramsundarahettige C, Gajalakshmi V, Aleksandrowicz L, Badwe R, Kumar R, Roy S, Suraweera W, Bray F, Mallath M, Singh PK, Sinha DN, Shet AS, Gelband H, Jha P; Million Death Study Collaborators. Cancer mortality in India: a nationally representative survey. Lancet 2012; 379: 1807-16.

[22]   Rutovskikh V, Asamoto M, Takasuka N, Murakoshi M, Nishino H, Tsuda H. Differential dose-dependent effects of alpha-, beta-carotenes and lycopene on gap-junctional intercellular communication in rat liver in vivo. Jpn J Cancer Res 1997; 88: 1121-24.

[23]   Levy J, Bosin E, Feldman B, Giat Y, Miinster A, Danilenko M, Sharoni Y. Lycopene is a more potent inhibitor of human cancer cell proliferation than either α or ß-carotene. Nutr Cancer 1995; 24: 257-266.

[24]   Hyang-Sook K, Bowen P, Longwen C, Duncan C, Ghosh L. Effects of tomato sauce consumption on apoptotic cell death in prostate benign hyperplasia and carcinoma. Nutr Cancer 2003; 47: 40-47.

[25]   Tanaka T, Shnimizu M, Moriwaki H. Cancer chemoprevention by carotenoids. Molecules 2012; 17: 3202-42.

[26]   Kurihara H, Koda H, Asami S, Kiso Y, Tanaka T. Contribution of the antioxidative property of astaxanthin to its protective effect on the promotion of cancer metastasis in mice treated with restraint stress. Life Sci 2002; 70: 2509-20.

[27]   Hecht SS. Chemoprevention by Isothiocyanates. In: Kelloff GJ, Hawk ET, Sigman CC, editors. Promising cancer chemopreventive agents, volume 1: cancer chemopreventive agents. New Jersey: Humana Press; 2004.

[28]   Conaway CC, Yang YM, Chung FL. Isothiocyanates as cancer chemopreventive agents: their biological activities and metabolism in rodents and humans. Curr Drug Metab 2002; 3: 233-55.

[29]   Kurahashi N, Iwasaki M, Sasazuki S, Otani T, Inoue M, Tsugane S; Japan Public Health Center-Based Prospective Study Group. Soy product and isoflavones consumption in relation to prostate cancer in Japanese men. Cancer Epidemiol Biomarks Prev 2007; 16: 538-45.

[30] Plochmann K, Korte G, Koutsilieri E, Richling E, Riederer P, Rethwilm A, Schreier P, Scheller C. Structure-activity relationships of flavonoid-induced cytotoxicity on human leukemia cells. Arch Biochem Biophys 2007; 460: 1-9.

[31] Kumar M, Kumar A, Nagpal R, Mohania D, Behare P, Verma V, Kumar P, Poddar D, Aggarwal PK, Henry CJ, Jain S, Yadav H. Cancer-preventing attributes of probiotics: an update. Int J Food Sci Nutr 2010; 61: 473-96.

[32] Limer JL, Spiers V. Phyto-estrogens and breast cancer chemoprevention. Breast Cancer Res 2004; 6: 119-127.

[33] Wakai K, Date C, Fukui M, Tamakoshi K, Watanabe Y, Hayakawa N, Kojima M, Kawado M, Suzuki KM, Hashimoto S, Tokudome S, Ozasa K, Suzuki S, Toyoshima H, Ito Y, Tamakoshi A. Dietary fiber and risk of colorectal cancer in the Japan collaborative cohort study. Cancer Epidemiol Biomarkers Prev 2007; 16: 668-675.

[34] Bidoli E, Talamini R, Bosetti C, Negri E, Maruzzi D, Montella M, Franceschi S, La Vecchia C. Macronutrients, fatty acids, cholesterol and prostate cancer risk. Ann Oncol 2005; 16: 152-57.

[35] Shannon J, King IB, Moshofsky R, Lampe JW, Gao DL, Ray RM, Thomas DB. Erythrocyte fatty acids and breast cancer risk: a case-control study in Shanghai, China. Am J Clin Nutr 2007; 85: 1090-1097.

[36] Naguib YM. Antioxidant activities of astaxanthin and related carotenoids. J Agric Food Chem 2000; 48: 1150-4.

[37] Yuan JP, Peng J, Yin K, Wang JH. Potential health-promoting effects of astaxanthin: a high value carotenoid mostly from microalgae. Mol Nutr Food Res 2011; 55: 150-165.

[38] Karppi J, Rissanen TH, Nyyssonen K, Olsson AG, Voutllainen S, Salonen JT. Effects of astaxanthin supplementation on lipid peroxidation. Int J Vitam Nutr Res 2007; 77: 3-11.

[39] Yoshida H, Yanai H, Ito K, Tomono Y, Koikeda T, Tsukahara H, Tada N. Administration of natural astaxanthin increases serum HDL-cholesterol and adiponectin in subjects with mild hyperlipidemia. Atherosclerosis 2010; 209: 520-523.

[40] Du H, Bennett D, Li L, Whitlock G, Guo Y. Physical activity and sedentary leisure time and their associations with BMI, waist circumference, and percentage body fat in 0.5 million adults: the China Kadoorie Biobank Study. Am J Clin Nutr 2013; 97: 487-96.

[41] Nakagawa K, Kiko T, Miyazawa T, Carpentero Burdeos G, Kimura F, Satoh A, Miyazawa T. Antioxidant effect of astaxanthin on phospholipids peroxidation in human erythrocytes. Br J Nutr 2011; 31: 1-9.

[42] Lockwook SF, Gross GJ. Disodium disuccinate astaxanthin (Cardax): antioxidant and anti-inflammatory cardio protection. Cardiovasc Drug Rev 2005; 23: 199-216.

[43] Kim JH, Kim YS, Song GG, Park JJ, Chang HI. Protective effect of astaxanthin on naproxen-induced gastric antral ulceration in rats. Eur J Pharmacol 2005; 514: 53-59.

[44] Nishikawa Y, Minenaka Y, Ichimura M, Tatsumi K, Nadamoto T, Urabe K. Effects of astaxanthin and vitamin C on the prevention of gastric ulcerations in stressed rats. J Nutr Sci Vitaminol (Tokyo) 2005; 51: 135-41.

[45] Gajalakshmi V, Whitlock G, Peto R. Social inequalities, tobacco chewing, and cancer mortality in south India: a case-control analysis of 2,580 cancer deaths among non-smoking non-drinkers. Cancer Causes Control 2012; 23 Suppl 1: 91-98.

[46] Chew B, Park J, Wong M, Wong TA. Comparison of the anticancer activities of dietary β-carotene, canthaxanthin and astaxanthin in mice in vivo. Anticancer Res 1999; 19: 1849-53.

[47] Jyonouchi H, Sun S, Iijima K, Gross M. Antitumor activity of astaxanthin and its mode of action. Nutr Cancer 2000; 36: 59-65.

[48] Tanaka T, Makita H, Ohnishi M, Mori H, Satoh K, Hara A. Chemoprevention of rat oral carcinogenesis by naturally occurring xanthophylls, astaxanthin and canthaxanthin. Cancer Res 1995; 55: 4059-64.

[49] Galagan SR, Paul P, Menezes L, LaMontagne DS. Influences on parental acceptance of HPV vaccination in demonstration projects in Uganda and Vietnam. Vaccine 2013; 31: 3072-78.

[50] Pashkow FJ, Watumull DG, Campbell CL. Astaxanthin: a novel potential treatment for oxidative stress and inflammation in cardiovascular disease. Am J Cardiol 2008; 101: 58D-68D.

[51] Kozuki Y, Miura Y, Yagasaki K. Inhibitory effects of carotenoids on the invasion of rat ascites hepatoma cells in culture. Cancer Lett 2000; 151: 111-18.

[52] Tanaka T, Morishita Y, Suzui M, Kojima T, Okumura A, Mori H. Chemoprevention of mouse urinary bladder carcinogenesis by the naturally occurring carotenoid astaxanthin. Carcinogen 1994; 15: 15-19.

[53] Tanaka T, Makita H, Ohnishi M, Mori H, Satoh K, Hara A. Chemoprevention of rat oral carcinogenesis by naturally occurring xanthophylls, astaxanthin and canthaxanthin. Cancer Res 1995a; 55: 4059-64.

[54] Tanaka T, Kawamori T, Ohnishi M, Makita H, Mori H, Satoh K, Hara A. Suppression of azoxymethane-induced rat colon carcinogenesis by dietary administration of naturally

occurring xanthophylls astaxanthin and canthaxanthin during the post initiation phase. Carcinogen 1995; 16: 2957-63.

[55] Levy J, Feldman B, Giat Y, Miinster A. Lycopene and astaxanthin inhibit human prostate cancer cell proliferation induced by androgens, presented at 13th Int. Carotenoid Symp., Honolulu, January 2002; 6:111: 35.

[56] Yasui Y, Hosokawa M, Mikami N, Miyashita K, Tanaka T. Dietary astaxanthin inhibits colitis and colitis-associated colon carcinogenesis in mice via modulation of the inflammatory cytokines. Chem Biol Interact 2011; 193: 79-87.

[57] McCarty MF. Minimizing the cancer-promotional activity of cox-2 as a central strategy in cancer prevention. Med Hypotheses 2011; 78: 45-57.

[58] Nagendraprabhu P, Sudhandiran G. Astaxanthin inhibits tumor invasion by decreasing extracellular matrix production and induces apoptosis in experimental rat colon carcinogenesis by modulating the expressions of ERK-2, NFkB and COX-2. Invest N Drug 2011; 29: 207-224.

[59] Gradelet S, Le Bon AM, Berges R, Suschetet M, Astorg P. Dietary carotenoids inhibit aflatoxin B1-induced liver preneoplastic foci and DNA damage in the rat: role of the modulation of aflatoxin B1 metabolism. Carcinogen 1998; 19: 403-411.

[60] Hix LM, Frey DA, McLaws MD, Østerlie M, Lockwood SF, Bertram JS. Inhibition of chemically-induced neoplastic transformation by a novel tetrasodium diphosphate astaxanthin derivative. Carcinogen 2005; 26: 1634-41.

[61] Kim HW, Park JS, Chew BP. β-carotene and astaxanthin inhibit mammary tumor cell growth and induce apoptosis in mice in vitro. FASEB J 2001; 15: A298-306.

[62] Sun S, Zhang R, Lee DS. Anti-tumor activity of astaxanthin on Meth-A tumor cells and its mode of action. FASEB J 1998; 12: 966-1003.

[63] Lee SH, Kolonel LN, Wilkens LR. Inhibition of benzo (a) pyrene-induced mouse fore stomach neoplasia by astaxanthin containing egg yolks. Agric Chem Biotechnol 1997; 40: 490-501.

[64] Lee SH, Lee BM, Park KK. Inhibition of sarcoma-180 cell-induced mouse ascites cancer by astaxanthin-containing egg yolks. J Kor Soc Food Sci Nutr 1998; 27: 163-69.

[65] Lyons NM, O Brien NM. Modulatory effects of an algal extract containing astaxanthin on UVA-irradiated cells in culture. J Dermatol Sci 2002; 30: 73-85.

[66] Savouré N, Bianchi A, Arnaboldi A. Vitamin A status and metabolism of cutaneous polyamines in the hairless mouse after UV irradiation: action of β-carotene and astaxanthin. Int J Vit Nutr Res 1995; 65: 79-85.

[67] Agarwal S, Rao AV. Carotenoids and chronic diseases. Drug Metabol Drug Interact 2000; 17: 189-210.

[68] Stahl W, Sies H. Lycopene: a biologically important carotenoid for humans? Arch Biochem Biophys 1996; 336: 1-9.

[69] Shi J, Le Maguer M. Lycopene in tomatoes: chemical and physical properties affected by food processing. Crit Rev Food Sci Nutr 2000; 40: 1-42.

[70] Porrini M, Riso P, Testolin G. Absorption of lycopene from single or daily portions of raw and processed tomato. Br J Nutr 1998; 80: 353-61.

[71] Fuhrman B, Elis A, Aviram M. Hypocholesterolemic effect of lycopene and beta-carotene is related to suppression of cholesterol synthesis and augmentation of LDL receptor activity in macrophages. Biochem Biophys Res Commun 1997; 233: 658-62.

[72] Rissanen TH, Voutilainen S, Nyyssonen K. Low serum lycopene concentration is associated with an excess incidence of acute coronary events and stroke: the Kuopio Ischaemic Heart Disease Risk Factor Study. Br J Nutr 2001; 85: 749-754.

[73] Sesso HD, Buring JE, Norkus EP, Gaziano JM. Plasma lycopene, other carotenoids and retinol and the risk of cardiovascular disease in women. Am J Clin Nutr 2004; 79: 47-53.

[74] Voutilainen S, Nurmi T, Mursu J, Rissanen TH. Carotenoids and cardiovascular health. Am J Clin Nutr 2006; 83: 1265-71.

[75] Yaping Z, Wenlia Y, Weile K, Ying Y. Anti-inflammatory and anticoagulant activities of lycopene in mice. Nutr Res 2003; 23: 591-1595.

[76] Nishino H, Tokuda H, Satomi Y, Masuda M, Bu P, Onozuka M, Yamaguchi S, Okuda Y, Takayasu J, Tsurata J, Okada M, Ichiishi E, Murakoshi M, Kato T, Misawa N, Narisawa T, Takasuka N, Yano M. Cancer prevention by carotenoids. Pure Appl Chem 1999; 71: 2273-2278.

[77] Okajima E, Ozono S, Endo T, Majima T, Tsutsumi M, Fukuda T, Akai H, Denda A, Hirao Y, Okajima E. Chemopreventive efficacy of piroxicam administered alone or in combination with lycopene and beta-carotene on the development of rat urinary bladder carcinoma after N-butyl-N-(4-hydroxybutyl)nitrosamine treatment. Jpn J Cancer Res 1997; 88: 543-552.

[78] Velmurugan B, Mani A, Nagini S. Combination of S-allylcysteine and lycopene induces apoptosis by modulating Bcl-2, Bax, Bim and caspases during experimental gastric carcinogenesis. Eur J Cancer Prev 2005; 14: 387-393.

[79] Heber D, Lu QY. Overview of mechanisms of action of lycopene. Exp Biol Med 2002; 227: 920-23.

[80] Sharoni Y, Danilenko M, Walfisch S, Amir H, Nahum A, Ben-Dor A, Hirsch K, Khanin M, Steiner M, Agemy L, Zango G, Levy J. Role of gene regulation in the anticancer activity of carotenoids. Pure Appl Chem 2002; 74: 1469-1477.

[81] Howlader N, Noone AM, Krapcho M, Garshell J, Neyman N. SEER cancer statistics review, 1975-2010.

[82] Kucuk O, Sarkar, FH, Sakr W, Djuric Z, Pollak MN, Khachik F, Li YW, Banerjee M, Grignon D, Bertram JS. Phase II randomized clinical trial of lycopene supplementation before radical prostatectomy. Cancer Epidemiol Biomarks Prev 2001; 10: 861-68.

[83] Karas M, Amir H, Fishman D, Danilenko M, Segal S, Nahum A, Koifmann A, Giat Y, Levy J, Sharoni Y. Lycopene interferes with cell cycle progression and insulin-like growth factor I signaling in mammary cancer cells. Nutr Cancer 2000; 36: 101-111.

[84] Lamontagne DS, Thiem VD, Huong VM, Tang Y, Neuzil KM. Immunogenicity of quadrivalent HPV vaccine among girls 11 to 13 Years of age vaccinated using alternative dosing schedules: results 29 to 32 months after third dose. J Infect Dis 2013; 208: 1325-34.

[85] Amir H, Karas M, Giat J, Danilenko M, Levy R, Yermiahu T, Levy J, Sharoni Y. Lycopene and 1, 25-dihydroxyvitamin D3 cooperate in the inhibition of cell cycle progression and induction of differentiation in HL-60 leukemic cells. Nutr Cancer 1999; 33: 105-12.

[86] Yang CM, Lu IH, Chen HY, Hu ML. Lycopene inhibits the proliferation of androgen-dependent human prostate tumor cells through activation of PPARγ-LXR-ABCA1 pathway. J Nutr Biochem 2012; 23: 8-17.

[87] Narisawa T, Fukaura Y, Hasebe M, Nomura S, Oshima S, Sakamoto H, Inakuma T, Ishiguro Y, Takayasu J, Nishino H. Prevention of Nmethylnitrosourea-induced colon carcinogenesis in F344 rats by lycopene and tomato juice rich in lycopene. Jpn J Cancer Res 1998; 89: 1003-1008.

[88] Watanabe S, Kitade Y, Masaki T, Nishioka M, Satoh K, Nishino H. Effects of lycopene and Sho-saiko-to on hepatocarcinogenesis in a rat model of spontaneous liver cancer. Nutr Cancer 2001; 39: 96-101.

[89] Lewington S, Li L, Sherliker P, Guo Y, Millwood I, Bian Z, Whitlock G, Yang L, Collins R, Chen J, Wu X, Wang S, Hu Y, Jiang L, Yang L, Lacey B, Peto R, Chen Z; China Kadoorie Biobank study collaboration. Seasonal variation in blood pressure and its relationship with outdoor temperature in 10 diverse regions of China: the China Kadoorie Biobank. J Hypertension 2012; 30: 1383-91.

[90] Faezizadeh Z, Mesbah-Namin SA, Gharib A, Saravani R, Godarzi M. Evaluating the effect of lycopene on telomerase activity in the human leukemia cell line K562. J Kashan Univer Med Sci 2012; 16: 398-405.

[91] Sommerburg O, Keunen JE, Bird AC, van Kuijk FJ. Fruits and vegetables that are sources for lutein and zeaxanthin: the macular pigment in human eyes. Br J Ophthalmol 1998; 82: 907-910.

[92] Kruger CL, Murphy M, DeFreitas Z, Pfannkuch F, Heimbach J. An innovative approach to the determination of safety for a dietary ingredient derived from a new source: case study using a crystalline lutein product. Food Chem Toxicol 2002; 40: 1535-49.

[93] Semba R, Dagnelie G. Are lutein and zeaxanthin conditionally essential nutrients for eye health? Med Hypotheses 2003; 61: 465-72.

[94] Alves-Rodrigues A, Shao A. The science behind lutein. Toxicol Lett 2004; 150: 57-83.

[95] Mezuk B, Chen Y, Yu C, Guo Y, Bian Z. Depression, anxiety, and prevalent diabetes in the Chinese population: findings from the China Kadoorie Biobank of 0.5 million people. J Psychosomatic Res 2013; 75: 511-17.

[96] González S, Astner S, Wu A, Goukassian D, Pathak M. Dietary lutein/zeaxanthin decreases ultraviolet B-induced epidermal hyperproliferation and acute inflammation in hairless mice. J Invest Dermatol 2003; 121: 399-405.

[97] Freudenheim JL, Marshall JR, Vena JE, Laughlin R, Brasure JR, Swanson MK, Nemoto T, Graham S. Premenopausal breast cancer risk and intake of vegetables, fruits, and related nutrients. J Natl Cancer Inst 1996; 88: 340-48.

[98] Iannone A, Rota C, Bergamini S, Tomasi A, Canfield LM. Antioxidant activity of carotenoids: an electron-spin resonance study on β-carotene and lutein interaction with free radicals generated in a chemical system. J Biochem Mol Toxicol 1998; 12: 299-304.

[99] Sujak A, Gabrielska J, Grudzinski W, Borc R, Mazurek P, Gruszecki WI. Lutein and zeaxanthin as protectors of lipid membranes against oxidative damage: the structural aspects. Arch Biochem Biophys 1999; 371: 301-7.

[100] Haegele AD, Gillette C, O'Neill C, Wolfe P, Heimendinger J, Sedlacek S, Thompson HJ. Plasma xanthophyll carotenoids correlate inversely with indices of oxidative DNA damage and lipid peroxidation. Cancer Epidemiol Biomarks Prev 2000; 9: 421-425.

[101] Stahl W, Junghans A, de Boer B, Driomina ES, Briviba K, Sies H. Carotenoid mixtures protect multilamellar liposomes against oxidative damage: synergistic effects of lycopene and lutein. FEBS Lett 1998; 427: 305-8.

[102] Gonzalez de Mejia E, Loarca-Pina G, Ramos-Gomez M. Antimutagenicity of xanthophylls present in Aztec Marigold (*Tageteserecta*) against 1-nitropyrene. Mutat Res 1997; 389: 219-26.

[103] Gonzalez de Mejia E, Ramos-Gomez M, Loarca-Pina G. Antimutagenic activity of natural xanthophylls against aflatoxin B1 in Salmonella typhimurium. Environ Mol Mutagen 1997; 30: 346-53.

[104] Park JS, Chew BP, Wong TS, Zhang JX, Magnuson NS. Dietary lutein but not astaxanthin or β-carotene increases pim-1 gene expression in murine lymphocytes. Nutr Cancer 1999; 33: 206-12.

[105] Millwood IY, Li L, Smith M, Guo Y, Yang L. Alcohol consumption in 0.5 million people from 10 diverse regions of China: prevalence, patterns, and socio-demographic and health-related correlates. Int J Epidemiol 2013; 42: 816-27.

[106] Narisawa T, Fukaura Y, Hasebe M, Ito M, Aizawa R, Murakoshi M, Uemura S, Khachik F, Nishino H. Inhibitory effects of natural carotenoids, α-carotene, β-carotene, lycopene and lutein, on colonic aberrant crypt foci formation in rats. Cancer Lett 1996; 107: 137-42.

[107] Le Marchand L, Hankin JH, Bach F, Kolonel LN, Wilkens LR, Stacewicz-Sapuntzakis M, Bowen PE, Beecher GR, Laudon F, Baque P. An ecological study of diet and lung cancer in the South Pacific. Int J Cancer 1995; 63: 18-23.

[108] Slattery ML, Benson J, Curtin K, Ma KN, Schaeffer D, Potter JD. Carotenoids and colon cancer. Am J Clin Nutr 2000; 71: 575-582.

[109] Park JS, Chew BP, Wong TS. Dietary lutein from marigold extract inhibits mammary tumor development in BALB/c mice. J Nutr 1998; 128: 1650-56.

[110] Sumantran VN, Zhang R, Lee DS, Wicha MS. Differential regulation of apoptosis in normal *versus* transformed mammary epithelium by lutein and retinoic acid. Cancer Epidemiol Biomarks Prev 2000; 9: 257-63.

[111] Dorgan JF, Sowell A, Swanson CA, Potischman N, Miller R, Schussler N, Stephenson HE. Relationships of serum carotenoids, retinol, α-tocopherol, and selenium with breast cancer risk: results from a prospective study in Columbia, Missouri (United States). Cancer Causes Control 1998; 9: 89-97.

[112] Thun MJ, Carter BD, Feskanich D, Freedman ND, Prentice R. 50-Year trends in smoking-related mortality in the United States. N Engl J Med 2013; 368: 351-64.

[113] Zhang S, Tang G, Russell RM, Mayzel KA, Stampfer MJ, Willett WC, Hunter DJ. Measurement of retinoids and carotenoids in breast adipose tissue and a comparison of concentrations in breast cancer cases and control subjects. Am J Clin Nutr 1997; 66: 626-32.

[114] Zhang S, Hunter DJ, Forman MR, Rosher BA, Speizer FE, Colditz GA, Manson DE, Hankinson SE, Willet WC. Dietary carotenoids and vitamins A, C, and E and risk of breast cancer. J Natl Cancer Inst 1999; 91: 547-56.

[115] Gunasekera RS, Sewgobind K, Desai S, Dunn L, Black HS, McKeehan WL, Patil B. Lycopene and lutein inhibit proliferation in rat prostate carcinoma cells. Nutr Cancer 2007; 58: 171-77.

[116] Chethan Kumar M, Veerabasappa Gowda T. Sunflower *(Helianthus annuus* L.) petals: a new biological source of lutein. Res J Pharma Biol Chem Sci 2010; 1: 438-48.

[117] Soon Park J, Chew BP, Wong TS. Dietary lutein from marigold extract inhibits mammary tumor development in BALB/c mice. J Nutr 1998; 31: 1650-1656.

[118] Wang XD, Krinsky NI. The bioconversion of β-carotene into retinoids. Subcell Biochem 1998; 30: 159-80.

[119] Wang XD, Tang GW, Fox JG, Krinsky NI, Russell RM. Enzymatic conversion of β-carotene into β-apo-carotenals and retinoids by human, monkey, ferret, and rat tissues. Arch Biochem Biophys 1991; 285: 8-16.

[120] Kiefer C, Hessel S, Lampert JM, Vogt K, Lederer MO, Breithaupt DE, von Lintig J. Identification and characterization of a mammalian enzyme catalyzing the asymmetric oxidative cleavage of provitamin A. J Biol Chem 1991; 276: 14110-116.

[121] Clevidence BA, Bieri JG. Associations of carotenoids with human plasma lipoproteins. In: Abelson JN, Simon MI, editors. Methods in enzymology. San Diego, CA, USA: Academic Press; 1993. pp. 33-46.

[122] Wang W, Connor SL, Johnson EJ, Klein ML, Hughes S, Connor WE. Effect of dietary lutein and zeaxanthin on plasma carotenoids and their transport in lipoproteins in age-related macular degeneration. Am J Clin Nutr 2007; 85: 762-69.

[123] Donaldson MS. Nutrition and cancer: a review of the evidence for an anti-cancer diet. Nutr J 2004; 3: 19-25.

[124] Murakoshi M, Nishino H, Satomi Y, Takayasu J, Hasegawa T, Tokuda H, Iwashima A, Okuzumi J, Okabe H, Kitano H. Potent preventive action of α-carotene against carcinogenesis: spontaneous liver carcinogenesis and promoting stage of lung and skin carcinogenesis in mice are suppressed more effectively by α-carotene than by β-carotene. Cancer Res 1992; 52: 6583-87.

[125] Prakash P, Liu C, Hu KQ, Krinsky NI, Russell RM, Wang XD. β-Carotene and β-apo-14'-carotenoic acid prevent the reduction of retinoic acid receptor β in benzo[a] pyrene-treated normal human bronchial epithelial cells. J Nutr 2004; 134: 667-73.

[126] Stivala LA, Savio M, Quarta S, Scotti C, Cazzalini O, Rossi L, Scovassi IA, Pizzala R, Melli R, Bianchi L. The antiproliferative effect of β-carotene requires p21waf1/cip1 in normal human fibroblasts. Eur J Biochem 2000; 267: 2290-96.

[127] Burton GW, Ingold KU. β-carotene: an unusual type of lipid antioxidant. Sci 1984; 224: 569-76.

[128] Zhang P, Omaye ST. β-carotene and protein oxidation: effects of ascorbic acid and α-tocopherol. Toxicol 2000; 146: 37-45.

[129] Paolini M, Ozono S, Endo T. β-carotene: a cancer chemopreventive agent or a co-carcinogen? Mutat Res 2003; 543: 195-203.

[130] Toniolo P, Van Kappel AL, Akhmedkhanov A, Ferrari P, Kato I, Shore RE, Riboli E. Serum carotenoids and breast cancer. Am J Epidemiol 2001; 153: 1142-7.

[131] Potischman N, McCulloch CE, Byers T. Breast cancer and dietary and plasma concentrations of carotenoids and vitamin A. Am J Clin Nutr 1990; 52: 909-15.

[132] Torun M, Yardim S, Gonenc A. Serum beta-carotene, vitamin E, vitamin C and malondialdehyde levels in several types of cancer. J Clin Pharm Ther 1995; 20: 259-63.

[133] Ramaswamy G, Krishnamoorthy L. Serum carotene, vitamin A, and vitamin C levels in breast cancer and cancer of the uterine cervix. Nutr Cancer 1996; 25: 173-177.

[134] Ziegler RG, Mayne ST, Swanson CA. Nutrition and lung cancer. Cancer Causes Control 1996; 7: 157-177.

[135] Heinonen OP, Albanes D. The effect of vitamin E and β carotene on the incidence of lung cancer and other cancers in male smokers. The α-Tocopherol, β Carotene Cancer Prevention Study Group. N Engl J Med 1994; 330: 1029-35.

[136] Hennekens CH, Buring JE, Manson JE, Stampfer M, Rosner B, Cook NR, Belanger C, LaMotte F, Gaziano JM, Ridker PM. Lack of effect of long-term supplementation with β carotene on the incidence of malignant neoplasms and cardiovascular disease. N Engl J Med 1996; 334: 1145-1149.

[137] Omenn GS, Goodman GE, Thornquist MD, Balmes J, Cullen MR, Glass A, Keogh JP, Meyskens FL, Valanis B, Onogi N, Takahashi T, Yamane T. Antiproliferative effect of carotenoids on human colon cancer cells without

[138] conversion to retinoic acid. Nutr Cancer 1998; 32: 20-31.

[138] Wang XD, Russell RM. Procarcinogenic and anticarcinogenic effects of β-carotene. Nutr Rev 1999; 57: 263-72.

[139] Rautalahti MT, Virtamo JR, Bennett M, Caderni G. The effects of supplementation with a-tocopherol and b-carotene on the incidence and mortality of carcinoma of the pancreas in a randomized, controlled trial. Cancer 1999; 86: 37-42.

[140] Jayappriyan KR, Rajkumar R, Venkatakrishnan V, Nagaraj S, Rengasamy R. In vitro anticancer activity of natural β-carotene from Dunaliella salina EU5891199 in PC-3 cells. Biomed Prevent Nutr 2013; 3: 99-105.

[141] Liu RH. Whole grain phytochemicals and health. J Cereal Sci 2007; 46: 207-19.

[142] Landrum JT, Bone RA, Herrero C. Astaxanthin, β-cryptoxanthin, lutein, and zeaxanthin. In: Meskin MS, editor. Phytochemicals in nutrition and health. Boca Raton, Florida: CRC Press; 2002. pp. 12.

[143] Mangels AR, Choi J, Pothoulakis C. Carotenoid content of fruits and vegetables: an evaluation of analytic data. J Am Diet Assoc 1993; 93: 284-295.

[144] Astorg P. Food carotenoids and cancer prevention: an overview of current research. Trends Food Sci Technol 1997; 8: 406-13.

[145] Yamaguchi M, Uchiyama S. Effect of carotenoid on calcium content and alkaline phosphatase activity in rat femoral tissues in vitro: the unique anabolic effect of beta-cryptoxanthin. Biol Pharm Bull 2003; 26: 1188-91.

[146] Sugiura M, Nakamura M, Ikoma Y, Yano M, Ogawa K, Matsumoto H, Kato M, Ohshima M, Nagao A. High serum carotenoids are inversely associated with serum gamma-glutamyltransferase in alcohol drinkers within normal liver function. J Epidemiol 2005; 15: 180-6.

[147] Sugiura M, Nakamura M, Ikoma Y, Yano M, Ogawa K, Matsumoto H, Kato M, Ohshima M, Nagao A. Serum carotenoid concentrations are inversely associated with serum aminotransferases in hyperglycemic subjects. Diabetes Res Clin Pract 2006; 71: 82-91.

[148] Faure H, Fayol V, Galabert C, Grolier P, Le Moël G, Steghens JP, Van Kappel A, Nabet F. [Carotenoids: 1. Metabolism and physiology]. Ann Biol Clin (Paris) 1999; 57: 169-83.

[149] Tanaka T, Sugiura H, Inaba R, Nishikawa A, Murakami A, Koshimizu K, Ohigashi H. Immunomodulatory action of citrus auraptene on macrophage functions and cytokine production of lymphocytes in female BALB/c mice. Carcinogen 1999; 20: 1471-76.

[150] Narisawa T, Fukaura Y, Oshima S, Inakuma T, Yano M, Nishino H. Chemoprevention by the

oxygenated carotenoid β-cryptoxanthin of N-methylnitrosourea induced colon carcinogenesis in F344 rats. Jpn J Cancer Res 1999; 90: 1061-65.

[151] Suzuki R, Kohno H, Yasui Y, Hata K, Sugie S, Miyamoto S, Sugawara K, Sumida T, Hirose Y, Tanaka T. Diet supplemented with citrus unshiu segment membrane suppresses chemically induced colonic preneoplastic lesions and fatty liver in male db/db mice. Int J Cancer 2007; 120: 252-58.

[152] Batieha AM, Astorg P, Shigenaga MK. Serum micronutrients and the subsequent risk of cervical cancer in a population-based nested case-control study. Cancer Epidemiol Biomarkers Prev 1993; 2: 335-44.

[153] Nishino H, Tokuda H, Satomi Y. Cancer prevention by carotenoids and curcumins. In: Bidlack WR, Tokuda H, Satomi Y, editors. Phytochemicals as bioactive agents. Lancaster, Pennsylvania: Technomic Publishing Company; 2000. pp. 9.

[154] Voorrips LE, Brants HA, Kardinaal AF. A prospective cohort study on antioxidant and folate intake and male lung cancer risk. Cancer Epidemiol Biomarkers Prev 2000; 9: 357-64.

[155] Baker RTM. Canthaxanthin in aqua feed applications: is there any risk? Trends Food Sci Technol 2002; 12: 240-248.

[156] Bertram JS, Pung A, Churley M, Kappock TJ, Wilkins LR, Cooney RV. Diverse carotenoids protect against chemically induced neoplastic transformation. Carcinogen 1991; 12: 671-78.

[157] Mathews-Roth MM, Krinsky NI. Carotenoid dose level and protection against UV-B induced skin tumors. Photochem Photobiol 1985; 42: 35-58.

[158] Zhang LX, Cooney RV, Bertram JS. Carotenoids up-regulate Connexin43 gene expression independent of their provitamin A or antioxidant properties. Cancer Res 1992; 52: 5707-15.

[159] Hanusch M, Gillette C, O'Neill C. Induction of gap junctional communication by 4-oxoretinoic acid generated from its precursor canthaxanthin. Arch Biochem Biophys 1995; 317: 423-35.

[160] Martin HD, Choi J, Pothoulakis C. Anti- and prooxidant properties of carotenoids. J Prakt Chem 1999; 341: 302-15.

[161] Beutner S, Pung A, Churley M, Kappock TJ. Quantitative assessment of antioxidant properties of natural colorants and phytochemicals: carotenoids, flavonoids, phenols and indigoids. The role of β-carotene in antioxidant functions. J Sci Food Agric 2001; 81: 559-65.

[162] Gradelet S, Sewgobind K, Desai S, Dunn L. Effects of canthaxanthin, astaxanthin, lycopene and lutein on liver xenobiotic-metaboliz-

[163] Jewell C, O'Brien NM. Effect of dietary supplementation with carotenoids on xenobiotic metabolizing enzymes in the liver, lung, kidney and small intestine of the rat. Br J Nutr 1999; 81: 235-43.

[164] Goralczyk R, Wu A, Goukassian D. Occurrence of birefringent retinal inclusions in cynomolgus monkeys after high doses of canthaxanthin. Invest Ophthalmol Vis Sci 1997; 38: 741-52.

[165] Gradelet S, Sewgobind K, Desai S, Dunn L. Modulation of aflatoxin B1 carcinogenicity, genotoxicity and metabolism in rat liver by dietary carotenoids: evidence for a protective effect of CYP1A inducers. Cancer Lett 1997; 114: 221-29.

[166] Leyon H, Giat Y, Miinster A. Reversibility of canthaxanthin deposits within the retina. Acta Ophthalmol 1990; 68: 607-615.

[167] Black HS, Mathews-Roth MM. Protective role of butylated hydroxytoluene and certain carotenoids in photocarcinogenesis. Photochem Photobiol 1991; 53: 707-16.

[168] Santamaria L, Bianchi A, Arnaboldi A, Ravetto C, Bianchi L, Pizzala R, Andreoni L, Santagati G, Bermond P. Chemoprevention of indirect and direct chemical carcinogenesis by carotenoids as oxygen radical quenchers. Ann N Y Acad Sci 1998; 534: 584-96.

[169] Grubbs CJ, Eto I, Juliana MM, Whitaker LM. Effect of canthaxanthin on chemically induced mammary carcinogenesis. Oncology 1991; 48: 239-45.

[170] Beppu F, Niwano Y, Tsukui T, Hosokawa M, Miyashita K. Single and repeated oral dose toxicity study of fucoxanthin (FX), a marine carotenoid, in mice. J Toxicol Sci 2009; 34: 501-10.

[171] Woo MN, Jeon SM, Shin YC, Lee MK, Kang MA, Choi MS. Anti-obese property of fucoxanthin is partly mediated by altering lipid-regulating enzymes and uncoupling proteins of visceral adipose tissue in mice. Mol Nutr Food Res 2009; 53: 1603-611.

[172] Das SK, Hashimoto T, Kanazawa K. Growth inhibition of human hepatic carcinoma HepG2 cells by fucoxanthin is associated with down-regulation of cyclin D. Biochem Biophys Acta 2008; 1780: 743-49.

[173] Hosokawa M, Kudo M, Maeda H, Kohno H, Tanaka T, Miyashita K. Fucoxanthin induces apoptosis and enhances the anti-proliferative effect of the PPAR gamma ligand, troglitazone, on colon cancer cells. Biochem Biophys Acta 2004; 1675: 113-19.

[174] Zhang Z, Zhang P, Hamada M, Takahashi S, Xing G, Liu J, Sugiura N. Potential chemopre-

vention effect of dietary fucoxanthin on urinary bladder cancer EJ-1 cell line. Oncol Rep 2008; 20: 1099-103.

[175] Kim JM, Araki S, Kim DJ, Park CB, Takasuka N, Baba-Toriyama H, Ota T, Nir Z, Khachik F, Shimidzu N. Chemopreventive effects of carotenoids and curcumins on mouse colon carcinogenesis after 1, 2-dimethylhydrazine initiation. Carcinogen 1998; 19: 81-85.

[176] Nishino H, Murakoshi M, Tokuda H, Satomi Y. Cancer prevention by carotenoids. Arch Biochem Biophys 2009; 483: 165-68.

[177] Okuzumi J, Takahashi T, Yamane T, Kitao Y, Inagake M, Ohya K, Nishino H, Tanaka Y. Inhibitory effects of fucoxanthin, a natural carotenoid, on N-ethyl-N'-nitro-N-nitrosoguanidine induced mouse duodenal carcinogenesis. Cancer Lett 1993; 68: 159-68.

[178] Miyashita K, Nishikawa S, Beppu F, Tsukui T, Abe M, Hosokawa M. The allenic carotenoid fucoxanthin, a novel marine nutraceutical from brown seaweeds. J Sci Food Agric 2011; 91: 1166-74.

[179] Liu CL, Huang YS, Hosokawa M, Miyashita K, Hu ML. Inhibition of proliferation of a hepatoma cell line by fucoxanthin in relation to cell cycle arrest and enhanced gap junctional intercellular communication. Chem Biol Interact 2009; 182: 165-72.

[180] Liu CL, Chiu YT, Hu ML. Fucoxanthin enhances HO-1 and NQO1 expression in murine hepatic BNL CL.2 cells through activation of the Nrf2/ARE system partially by its pro-oxidant activity. J Agric Food Chem 2011; 59: 11344-351.

[181] Murakami C, Takemura M, Sugiyama Y, Kamisuki S, Asahara H, Kawasaki M, Ishidoh T, Linn S, Yoshida S, Sugawara F. Vitamin A-related compounds, all-trans retinal and retinoic acids, selectively inhibit activities of mammalian replicative DNA polymerases. Biochem Biophys Acta 2012; 1574: 85-92.

[182] Yoshiko S, Hoyoku N. Fucoxanthin, a natural carotenoid, induces G1 arrest and GADD45 gene expression in human cancer cells. In Vivo 2007; 21: 305-309.

[183] Sangeetha RK, Bhaskar N, Baskaran V. Comparative effects of beta-carotene and fucoxanthin on retinol deficiency induced oxidative stress in rats. Mol Cell Biochem 2009; 331: 59-67.

[184] Urikura I, Sugawara T, Hirata T. Protective effect of Fucoxanthin against UVB-induced skin photoaging in hairless mice. Biosci Biotechnol Biochem 2011; 75: 757-60.

[185] Shimoda H, Tanaka J, Shan SJ. Anti-pigmentary activity of fucoxanthin and its influence on skin mRNA expression of melanogenic molecules. J Pharm Pharmacol 2010; 62: 1137-45.

[186] Satomi Y. Fucoxanthin induces GADD45A expression and G1 arrest with SAPK/JNK activation in LNCap human prostate cancer cells. Anticancer Res 2012; 32: 807-813.

[187] Kotake-Nara E, Asai A, Nagao A. Neoxanthin and fucoxanthin induce apoptosis in PC-3 human prostate cancer cells. Cancer Lett 2005; 220: 75-84.

[188] McNaughton SA, Marks GC. Development of a food composition database for the estimation of dietary intakes of glucosinolates, the biologically active constituents of cruciferous vegetables. Br J Nutr 2003; 90: 687-97.

[189] Rouzaud G, Young SA, Duncan AJ. Hydrolysis of glucosinolates to isothiocyanates after ingestion of raw or microwaved cabbage by human volunteers. Cancer Epidemiol Biomarkers Prev 2004; 13: 125-31.

[190] Singh SV, Singh K. Cancer chemoprevention with dietary isothiocyanates mature for clinical translational research. Carcinogen 2012; 33: 1833-1842.

[191] Navarro SL, Li F, Lampe JW. Mechanisms of action of isothiocyanates in cancer chemoprevention: an update. Food Funct 2011; 2: 579-87.

[192] Chorley BN, Campbell MR, Wang X. Identification of novel NRF2-regulated genes by ChIP-Seq: influence on retinoid X receptor alpha. Nucleic Acids Res 2012; 40: 7416-29.

[193] Lee JS, Surh YJ. Nrf2 as a novel molecular target for chemoprevention. Cancer Lett 2005; 224: 171-84.

[194] Wagner AE, Boesch-Saadatmandi C, Dose J. Anti-inflammatory role of Nrf2, NF-kB and microRNA-155. J Cell Mol Med 2012; 16: 836-43.

[195] Juge N, Mithen RF, Traka M. Molecular basis for chemoprevention by sulforaphane: a comprehensive review. Cell Mol Life Sci 2007; 64: 1105-27.

[196] Dashwood RH, Ho E. Dietary histone deacetylase inhibitors: from cells to mice to man. Sem Cancer Biol 2007; 17: 363-69.

[197] Marks PA, Xu WS. Histone deacetylase inhibitors: potential in cancer therapy. J Cell Biochem 2009; 107: 600-08.

[198] Seligson DB, Horvath S, Shi T, Yu H, Tze S, Grunstein M, Kurdistani SK. Global histone modification patterns predict risk of prostate cancer recurrence. Nature 2005; 435: 1262-266.

[199] Gamet-Payrastre L, Li P, Lumeau S, Cassar G, Dupont MA, Chevolleau S, Gasc N, Tulliez J, Tercé F. Sulforaphane, a naturally occurring isothiocyanate, induces cell cycle arrest and apoptosis in ht29 human colon cancer cells. Cancer Res 2013; 60: 1426-33.

[200] Wang M, Chen S, Wang S, Sun D, Chen J, Li Y, Han W, Yang X, Gao HQ. Effects of phytochemicals sulforaphane on uridine diphosphate-glucuronosyltransferase expression as well as cell-cycle arrest and apoptosis in human colon cancer Caco-2 cells. Chin J Physiol 2012; 55: 134-44.

[201] Tseng E, Scott-Ramsay EA, Morris ME. Dietary organic isothiocyanates are cytotoxic in human breast cancer MCF-7 and mammary epithelial MCF-12A cell lines. Exp Biol Med 2004; 229: 835-42.

[202] Normark S, Nilsson C, Normark BH, Hornef MW. Persistent infection with *Helicobacter pylori* and the development of gastric cancer. Adv Cancer Res 2003; 90: 63-89.

[203] Fahey JW, Haristoy X, Dolan PM, Kensler TW, Scholtus I, Stephenson KK, Talalay P, Lozniewski A. Sulforaphane inhibits extracellular, intracellular, and antibiotic-resistant strains of *helicobacter pylori* and prevents benzo[a]pyrene-induced stomach tumors. Proc Natl Acad Sci U S A 2002; 99: 7610-7615.

[204] Haristoy X, Angioi-Duprez K, Duprez A, Lozniewski A. Efficacy of sulforaphane in eradicating *Helicobacter pylori* in human gastric xenografts implanted in nude mice. Antimicrob Agents Chemother 2003; 47: 3982-84.

[205] Reed JC. Dysregulation of apoptosis in cancer. J Clin Oncol 1999; 17: 2941-53.

[206] Mi L, Hood BL, Stewart NA. Identification of potential protein targets of isothiocyanates by proteomics. Chem Res Toxicol 2011; 24: 1735-43.

[207] Wattenberg LW. Inhibition of carcinogenic effects of polycyclic hydrocarbons by benzyl isothiocyanate and related compounds. J Natl Cancer Inst 1997; 58: 395-398.

[208] Myzak MC, Dashwood WM, Orner GA, Ho E, Dashwood RH. Sulforaphane inhibits histone deacetylase *in vivo* and suppresses tumorigenesis in Apc-minus mice. FASEB J 2006; 20: 506-08.

[209] Meeran SM, Patel SN, Li Y, Shukla S, Tollefsbol TO. Bioactive dietary supplements reactivate ER expression in ER-negative breast cancer cells by active chromatin modifications. PLoS One 2012; 7: e377-48.

[210] Abbaoui B, Riedl KM, Ralston RA, Thomas-Ahner JM, Schwartz SJ, Clinton SK, Mortazavi A. Inhibition of bladder cancer by broccoli isothiocyanates sulforaphane and erucin: characterization, metabolism and interconversion. Mol Nutr Food Res 2000; 56: 1675-87.

[211] Chaudhuri D, Orsulic S, Ashok BT. Antiproliferative activity of sulforaphane in Akt-overexpressing ovarian cancer cells. Mol Cancer Ther 2007; 6: 334-45.

[212] Huang TY, Chang WC, Wang MY, Yang YR, Hsu YC. Effect of sulforaphane on growth inhibition in human brain malignant glioma GBM 8401 cells by means of mitochondrial- and MEK/ERK-mediated apoptosis pathway. Cell Biochem Biophys 2012; 63: 247-59.

[213] Liang H, Lai B, Yuan Q. Sulforaphane induces cell-cycle arrest and apoptosis in cultured human lung adenocarcinoma LTEP-A2 cells and retards growth of LTEP-A2 xenografts in vivo. J Nat Prod 2008; 71: 1911-14.

[214] Schrezenmeir J, de Vrese M. Probiotics, prebiotics and synbiotics-approaching a definition. Am J Clin Nutr 2001; 73 Suppl: 361S-364S.

[215] Ghosh S, van Heel D, Playford RJ. Probiotics in inflammatory bowel disease: is it all gut flora modulation? Gut 2004; 53: 620-22.

[216] Penner RM, Fedorak RN. Probiotics in the management of inflammatory bowel disease. Medscape General Med 2005; 7: 19-26.

[217] De Vrese M, Stegelmann A, Richter B, Fenselau S, Laue C, Schrezenmeir J. Probiotics-compensation for lactase insufficiency. Am J Clin Nutr 2001; 73 Suppl: 421S-29S.

[218] Pelletier X, Laure-Boussuge S, Donazzolo Y. Hydrogen excretion upon ingestion of dairy products in lactose-intolerant male subjects: importance of the live flora. Eur J Clin Nutr 2001; 55: 509-12.

[219] Parvez S, Malik KA, Kang SA, Kim HY. Probiotics and their fermented food products are beneficial for health. J Appl Microbiol 2006; 100: 1171-85.

[220] Sydorchuk L, Sydorchuk G, Sydorchuk I. Vascular pathology and immune disorders in hypertensive patients. Am J Hypertens 2005; 18: A49-A59.

[221] Nam H, Ha M, Bae O, Lee Y. Effect of Weissella confusa strain PL9001 on the adherence and growth of *Helicobacter pylori*. Appl Environ Microbiol 2002; 68: 4642-45.

[222] Sgouras D, Maragkoudakis P, Petraki K, Martinez-Gonzalez B, Eriotou E, Michopoulos S, Kalantzopoulos G, Tsakalidou E, Mentis A. In vitro and in vivo inhibition of *helicobacter pylori* by *Lactobacillus casei* strain Shirota. Appl Environ Microbiol 2004; 70: 518-526.

[223] Liong MT, Shah NP. Optimization of cholesterol removal by probiotics in the presence of prebiotics by using a response surface method. Appl Environ Microbiol 2005; 71: 1745-53.

[224] Pereira DI, McCartney AL, Gibson GR. An in vitro study of the probiotic potential of a bile-salt-hydrolyzing *Lactobacillus fermentum* strain, and determination of its cholesterol-lowering properties. Appl Environ Microbiol 2003; 69: 4743-52.

[225] Brown AC, Valiere A. Probiotics and medical nutrition therapy. Nutr Clin Care 2004; 7: 56-68.

[226] Ewaschuk JB, Walker JW, Diaz H, Madsen KL. Nutrient physiology, metabolism, and nutrient-nutrient interactions bioproduction of conjugated linoleic acid by probiotic bacteria occurs in-vitro and in-vivo in mice. J Nutr 2006; 136: 1483-1487.

[227] Rafter J, Bennett M, Caderni G, Clune Y, Hughes R, Karlsson PC, Klinder A, O'Riordan M, O'Sullivan GC, Pool-Zobel B, Rechkemmer G, Roller M, Rowland I, Salvadori M, Thijs H, Van Loo J, Watzl B, Collins JK. Dietary synbiotics reduce cancer risk factors in polypectomized and colon cancer patients. Am J Clin Nutr 2007; 85: 488-96.

[228] Wollowski I, Rechkemmer G, Pool-Zobel BL. Protective role of probiotics and prebiotics in colon cancer. Am J Clin Nutr 2001; 73: 451S-455S.

[229] Burns AJ, Rowland IR. Anti-carcinogenicity of probiotics and prebiotics. Curr Issues Intest Microbiol 2000; 1: 13-24.

[230] Rowland IR, Rumney CJ, Coutts JT, Lievense LC. Effect of Bifidobacterium longum and inulin on gut bacterial metabolism and carcinogen-induced aberrant crypt foci in rats. Carcinogen 1998; 19: 281-285.

[231] Challa A, Rao DR, Chawan CB, Shackelford L. Bifidobacterium longum and lactulose suppress azoxymethane-induced colonic aberrant crypt foci in rats. Carcinogen 1997; 207: 517-521.

[232] Ma EL, Choi YJ, Choi J, Pothoulakis C, Rhee SH, Im E. The anticancer effect of probiotic Bacillus polyfermenticus on human colon cancer cells is mediated through ErbB2 and ErbB3 inhibition. Int J Cancer 2010; 127: 780-90.

[233] Wade C, Kronenberg F, Kelly A, Murphy PA. Hormone-modulating herbs: implications for Women's Health. J Am Med Women Assoc 1999; 54: 181-3.

[234] Gardiner T, Ramberg J. Plant estrogens: importance in health and disease. Glycosci Nutr 2001; 2: 2-12.

[235] Roudsari AH, Tahbaz F, Hossein-Nezhad A, Arjmandi B, Larijani B, Kimiagar SM. Assessment of soy phytoestrogens' effects on bone turnover indicators in menopausal women with osteopenia in Iran: a before and after clinical trial. Nutr J 2005; 4: 30-39.

[236] Kronenberg F, Fugh-Berman A. Complementary and alternative medicine for menopausal symptoms: a review of randomized, controlled trials. Ann Int Med 2000; 137: 805-813.

[237] Ziegler RG. Phytoestrogens and breast cancer. Am J Clin Nutr 2004; 79: 183-184.

[238] Raffoul JJ, Wang Y, Kucuk O. Genistein inhibits radiation-induced activation of NF-kB in prostate cancer cells promoting apoptosis and G2/M cell cycle arrest. BMC Cancer 2006; 6: 107-115.

[239] Horn-Ross PL, Hoggatt KJ, Lee MM. Phytoestrogens and thyroid cancer risk: the San Francisco Bay Area thyroid cancer study. Cancer Epidemiol Biomarks Prev 2002; 11: 43-9.

[240] Widyarini S, Domanski D, Painter N, Reeve VE. Estrogen receptor signaling protects against immune suppression by UV radiation exposure. Proc Natl Acad Sci U S A 2006; 103: 12837-12842.

[241] Cotterchio M, Boucher BA, Manno M, Gallinger S, Okey A, Harper P. Dietary phytoestrogen intake is associated with reduced colorectal cancer risk. J Nutr 2006; 136: 3046-3053.

[242] Swami S, Krishnan AV, Peehl DM. Genistein potentiates the growth inhibitory effects of 1,25-dihydroxyvitamin D3 in DU145 human prostate cancer cells: role of the direct inhibition of CYP24 enzyme activity. Mol Cell Endocrinol 2005; 241: 49-61.

[243] Yeh TC, Chiang PC, Li TK, Hsu JL, Lin CJ, Wang SW, Peng CY, Guh JH. Genistein induces apoptosis in human hepatocellular carcinomas via interaction of endoplasmic reticulum stress and mitochondrial insult. Biochem Pharmacol 2007; 73: 782-792.

[244] Adlercreutz H, Markkanen H, Watanabe S. Plasma concentrations of phytoestrogens in Japanese men. Lancet 1993; 342: 1209-10.

[245] Wu AH, Ziegler RG, Horn-Ross PL. Tofu and risk of breast cancer in Asian-Americans. Cancer Epidemiol Biomarks Prev 1996; 5: 901-6.

[246] Kuiper GG, Lemmen JG, Carlsson B, Corton JC, Safe SH, van der Saag PT, van der Burg B, Gustafsson JK. Interaction of estrogenic chemicals and phytoestrogens with estrogen receptor beta. Endocrinol 1998; 139: 4252-63.

[247] Castillejo G, Bullo M, Anguera A, Escribano J, Salas-Salvado J. A controlled, randomized, double-blind trial to evaluate the effect of a supplement of cocoa husk that is rich in dietary fiber on colonic transit in constipated pediatric patients. Pediatrics 2006; 118: e641-e648.

[248] Malhotra S, Rana SV, Sinha SK, Khurana S. Dietary fiber assessment of patients with irritable bowel syndrome from northern India. Indian J Gastroenterol 2004; 23: 217-18.

[249] Van Rosendaal GM, Shaffer EA, Edwards AL, Brant R. Effect of time of administration on cholesterol-lowering by psyllium: a randomized cross-over study in normocholesterolemic or slightly hypercholesterelomic subjects. Nutr J 2004; 3: 17-25.

[250] Murakami K, Sasaki S, Okubo H, Takahashi Y, Hosoi Y, Itabashi M. Dietary fiber intake, di-

etary glycemic index and load, and body mass index: a cross-sectional study of 3931 Japanese women aged 18-20 years. Eur J Clin Nutr 2007; 61: 986-95.

[251] Hannan JM, Ali L, Rokeya B, Khaleque J, Akhter M. Flatt PR, Abdel-Wahab YH. Soluble dietary fiber fraction of *Trigonella foenum-graecum* (fenugreek) seed improves glucose homeostasis in animal models of type 1 and type 2 diabetes by delaying carbohydrate digestion and absorption, and enhancing insulin action. Br J Nutr 2007; 97: 514-21.

[252] Park Y, Brinton LA, Subar AF Hollenbeck A, Schatzkin A. Dietary fiber intake and risk of breast cancer in postmenopausal women: the National Institutes of Health-AARP Diet and Health Study. Am J Clin Nutr 2009; 90: 664-671.

[253] Schatzkin A, Park Y, Leitzmann MF, Hollenbeck AR, Cross AJ. Prospective study of dietary fiber, whole grain foods, and small intestinal cancer. Gastroenterol 2008; 135: 1163-167.

[254] Nomura AM, Hankin JH, Henderson BE, Wilkens LR, Murphy SP, Pike MC, Le Marchand L, Stram DO, Monroe KR, Kolonel LN. Dietary fiber and colorectal cancer risk: the multiethnic cohort study. Cancer Causes Control 2007; 18: 753-64.

[255] Raina K, Ravichandran K, Rajamanickam S. Inositol hexaphosphate inhibits tumor growth, vascularity, and metabolism in TRAMP mice: a multiparametric magnetic resonance study. Cancer Prev Res 2013; 6: 40-50.

[256] Simopoulos AP. Trans fatty acids. In: Spiller GA, editor. Handbook of lipids in human nutrition. Boca Raton: CRC Press; 1995. pp. 91-99.

[257] Takezaki T, Inoue M, Kataoka H. Diet and lung cancer risk from a 14-year population-based prospective study in Japan: with special reference to fish consumption. Nutr Cancer 2003; 45: 160-7.

[258] Voorrips LE, Brants HA, Kardinaal AF, Hiddink GJ, van den Brandt PA, Goldbohm RA. Intake of conjugated linoleic acid, fat, and other fatty acids in relation to postmenopausal breast cancer: the Netherlands Cohort Study on Diet and Cancer. Am J Clin Nutr 2002; 76: 873-82.

[259] Kenler AS, Swails WS, Driscoll DF. Early enteral feeding in postsurgical cancer patients: fish oil structured lipid-based polymeric formula versus a standard polymeric formula. Ann Surg 1996; 223: 316-33.

[260] McCarter MD, Gentilini OD, Gomez ME, Daly JM. Preoperative oral supplement with immuno-nutrients in cancer patients. JPEN J Parenter Enteral Nutr 1998; 22: 206-11.

[261] Gerber M. Omega-3 fatty acids and cancers: a systematic update review of epidemiological studies. Br J Nutr 2012; 107: S228-S239.

[262] Chyou PH, Nomura AMY, Stemmermann GN. Diet, alcohol, smoking and cancer of the upper aerodigestive tract: a prospective study among Hawaii Japanese men. Int J Cancer 1995; 60: 616-21.

[263] Chyou PH, Nomura AMY, Stemmermann GN. A prospective study of diet, smoking, and lower urinary tract cancer. Ann Epidemiol 1993; 3: 211-216.

[264] Shahidi F, Naczk M. Phenolics in food and nutraceuticals. Florida: CRC Press LLC; 2004.

[265] Beecher GR. Overview of dietary flavonoids: nomenclature, occurrence and intake. J Nutr 2003; 133: 3248S-54S.

[266] Kanerva A, Raki M, Ranki T, Sarkioja M, Koponen J, Desmond RA, Helin A, Stenman UH, Isoniemi H, Hockerstedt K, Ristimaki A, Hemminki A. Chlorpromazine and apigenin reduce adenovirus replication and decrease replication associated toxicity. J Gene Med 2007; 9: 3-9.

[267] Friedman M. Overview of antibacterial, antitoxin, antiviral, and antifungal activities of tea flavonoids and teas. Mol Nutr Food Res 2007; 51: 116-34.

[268] Zhou L, Li D, Wang J, Liu Y, Wu J. Antibacterial phenolic compounds from the spines of *Gleditsia Sinensis* Lam. Nat Prod Res 2007; 21: 283-291.

[269] Kawai M, Hirano T, Higa S, Arimitsu J, Maruta M, Kuwahara Y, Ohkawara T, Hagihara K, Yamadori T, Shima Y, Ogata A, Kawase I, Tanaka T. Flavonoids and related compounds as anti-allergic substances. Allergol Int 2007; 56: 113-123.

[270] Nowakowska Z. A review of anti-infective and anti-inflammatory chalcones. Eur J Med Chem 2007; 42: 125-37.

[271] Cogolludo A, Frazziano G, Briones AM, Cobeno L, Moreno L, Lodi F, Salaices M, Tamargo J, Perez-Vizcaino F. The dietary flavonoid quercetin activates bkca currents in coronary arteries via production of H2O2. Cardiovasc Res 2007; 73: 424-31.

[272] Gates MA, Tworoger SS, Hecht JL, De Vivo I, Rosner B, Hankinson SE. A prospective study of dietary flavonoid intake and incidence of epithelial ovarian cancer. Int J Cancer 2007; 121: 2225-32.

[273] Theodoratou E, Kyle J, Cetnarskyj R, Farrington SM, Tenesa A, Barnetson R, Porteous M, Dunlop M, Campbell H. Dietary flavonoids and the risk of colorectal cancer. Cancer Epidemiol Biomarkers Prev 2007; 16: 684-93.

[274] Hostanska K, Jurgenliemk G, Abel G, Nahrstedt A, Saller R. Willow bark extract (BNO1455) and its fractions suppress growth and induce apoptosis in human colon and lung cancer cells. Cancer Detect Prev 2007; 31: 129-39.

[275] Garavello W, Rossi M, McLaughlin J, Bosetti C, Negri E, Lagiou P, Talamini R, Franceschi S, Parpinel M Maso LD, La Vecchia C. Flavonoids and laryngeal cancer risk in Italy. Ann Oncol 2007; 18: 1104-1109.

[276] Ujiki MB, Ding XZ, Salabat MR, Bentrem DJ, Golkar L, Milam B, Talamonti MS, Bell RH, Iwamura T, Adrian TE. Apigenin inhibits pancreatic cancer cell proliferation through g2/m cell cycle arrest. Mol Cancer 2006; 5: 76-85.

[277] Rossi M, Garavello W, Talamini R, La Vecchia C, Franceschi S, Lagiou P, Zambon P, Dal Maso L, Bosetti C, Negri E. Flavonoids and risk of squamous cell esophageal cancer. Int J Cancer 2007; 120: 1560-1564.

[278] Fink BN, Steck SE, Wolff MS, Britton JA, Kabat GC, Schroeder JC, Teitelbaum SL, Neugut AI, Gammon MD. Dietary flavonoid intake and breast cancer risk among women on long Island. Am J Epidemiol 2007; 165: 514-523.

[279] Bosetti C, Rossi M, McLaughlin JK, Negri E, Talamini R, Lagiou P, Montella M, Ramazzotti V, Franceschi S, LaVecchia C. Flavonoids and the risk of renal cell carcinoma. Cancer Epidemiol Biomarkers Prev 2007; 16: 98-101.

[280] Kong AN, Owuor E, Yu R, Hebbar V, Chen C, Hu R, Mandlekar S. Induction of xenobiotic enzymes by the MAP kinase pathway and the antioxidant or electrophile response element (ARE/EpRE). Drug Metab Rev 2001; 33: 255-71.

[281] Xu C, Li CY, Kong AN. Induction of phase I, II and III drug metabolism/transport by xenobiotics. Arch Pharm Res 2005; 28: 249-268.

[282] Chang KL, Kung ML, Chow NH, Su SJ. Genistein arrests hepatoma cells at G2/M phase: involvement of ATM activation and up-regulation of p21waf1/cip1 and Wee1. Biochem Pharmacol 2004; 67: 717-26.

[283] Kanadaswami C, Lee LT, Lee PP, Hwang JJ, Ke FC, Huang YT. The antitumor activities of flavonoids. In Vivo 2000; 19: 895-909.

[284] Hou Z, Lambert JD, Chin KV, Yang CS. Effects of tea polyphenols on signal transduction pathways related to cancer chemoprevention. Mutat Res 2004; 555: 3-19.

[285] Adhami VM, Ahmad N, Mukhtar H. Molecular targets for green tea in prostate cancer prevention. J Nutr 2003; 133 Suppl: 2417S-24S.

[286] Shimizu M, Deguchi A, Lim JT, Moriwaki H, Kopelovich L, Weinstein IB. Epigallocatechin gallate and polyphenon E inhibit growth and activation of the epidermal growth factor receptor and human epidermal growth factor receptor-2 signaling pathways in human colon cancer cells. Clin Cancer Res 2005; 11: 2735-46.

[287] Wagner I, Greim C, Laufer S, Heide L, Gleiter CH. Influence of willow bark extract on cyclo-oxygenase activity and on tumor necrosis factor alpha or interleukin 1 beta release in vitro and ex vivo. Clin Pharmacol Ther 2003; 73: 272-4.

[288] Rao CV, Newmark HL, Reddy BS. Chemo-preventive effect of farnesol and lanosterol on colon carcinogenesis. Cancer Detect Prev 2002; 26: 419-25.

[289] Zhang H, Spitz MR, Tomlinson GE, Schabath MB, Minna JD, Wu X. Modification of lung cancer susceptibility by green tea extract as measured by the comet assay. Cancer Detect Prev 2002; 26: 4144-418.

[290] Li Y, Ahmed F, Ali S, Philip PA, Kucuk O, Sarkar FH. Inactivation of nuclear factor kappa B by soy isoflavone genistein contributes to increased apoptosis induced by chemotherapeutic agents in human cancer cells. Cancer Res 2005; 65: 6934-42.

[291] Kim HP, Mani I, Iversen L, Ziboh VA. Effects of naturally-occurring flavonoids and bioflavonoids on epidermal cyclooxygenase and lipoxygenase from guinea-pigs. Prostaglandins Leukot Essent Fatty Acids 1998; 58: 17-24.

[292] Yin F, Giuliano AE, Law RE, Van Herle AJ. Apigenin inhibits growth and induces G2/M arrest by modulating cyclin-cdk regulators and ERK MAP kinase activation in breast carcinoma cells. Anticancer Res 2001; 21: 413-420.

[293] Wang W, Heideman L, Chung CS, Pelling JC, Koehler KJ, Birt DF. Cell-cycle arrest at G2/M and growth inhibition by apigenin in human colon carcinoma cell lines. Mol Carcinog 2000; 28: 102-10.

[294] Neuhouser ML. Dietary flavonoids and cancer risk: evidence from human population studies. Nutr Cancer 2004; 50: 1-7.

[295] Hoensch HP, Kirch W. Potential role of flavonoids in the prevention of intestinal neoplasia: a review of their mode of action and their clinical perspectives. Int J Gastrointest Cancer 2005; 35: 187-95.

[296] Nagata C, Inaba S, Kawakami N, Kakizoe T, Shimizu H. Inverse association of soy product intake with serum androgen and estrogen concentrations in Japanese men. Nutr Cancer 2000; 36: 14-18.

[297] Holzbeierlein JM, McIntosh J, Thrasher JB. The role of soy phytoestrogens in prostate cancer. Curr Opin Urol 2005; 15: 17-22.

[298] Evans BA, Griffiths K, Morton MS. Inhibition of 5 a-reductase in genital skin fibroblasts and prostate tissue by dietary lignans and isoflavonoids. J Endocrinol 1995; 147: 295-302.

[299] Bylund A, Zhang JX, Bergh A. Rye bran and soy protein delay growth and increase apoptosis of

human LNCaP prostate adenocarcinoma in nude mice. Prostate 2000; 42: 304-14.

[300] Bingham SA, Day NE, Luben R. Dietary fibre in food and protection against colorectal cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC): an observational study. Lancet 2003; 361: 1496-501.

[301] Bingham S. The fibre-folate debate in colorectal cancer. Proc Nutr Soc 2006; 65: 19-23.

[302] Powers HJ. Interaction among folate, riboflavin, genotype, and cancer, with reference to colorectal and cervical cancer. J Nutr 2005; 135: 2960-6S.

[303] Farmer P, Frenk J, Knaul FM, Shulman LN, Alleyne G, Armstrong L, Atun R, Blayney D, Chen L, Feachem R, Gospodarowicz M, Gralow J, Gupta S, Langer A, Lob-Levyt J, Neal C, Mbewu A, Mired D, Piot P, Reddy KS, Sachs JD, Sarhan M, Seffrin JR. Expansion of cancer care and control in countries of low and middle income: a call to action. Lancet 2010; 376: 1186-93.

[304] Hunter DJ, Reddy KS. Non communicable diseases. N Engl J Med 2013; 369: 1336-43.