

## Review Article

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

Mohammad Aghajanpour<sup>1</sup>, Mohamad Reza Nazer<sup>2</sup>, Zia Obeidavi<sup>3</sup>, Mohsen Akbari<sup>4</sup>, Parya Ezati<sup>5</sup>, Nasroallah Moradi Kor<sup>6</sup>

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

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**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 increase 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 considered 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 maintain health and thereby reduce the risk of disease. There are some reported evidences showing association between functional foods and cancer. For example, S-allyl 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<sub>3</sub> 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 peroxy 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 increase 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**.

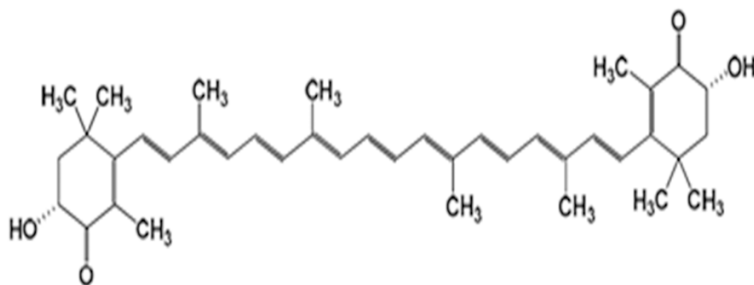
#### Function

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

## Functional foods and cancers

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

Functional foods	Dietary Sources	Function	Effects	References
$\alpha$ -Carotene	Yellow-orange and dark-green vegetables	Antioxidant	In moderate dose increase enhance gap junctional intercellular communication	[22]
$\beta$ -Carotene	Green leafy vegetables and orange and yellow fruits and vegetables	Antioxidant	Similar $\alpha$ -Carotene	[22]
Lycopene	Tomatoes, water melon, apricot, peaches	Antioxidant	Lycopene is more potent than $\alpha$ and $\beta$ -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]
$\beta$ -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.

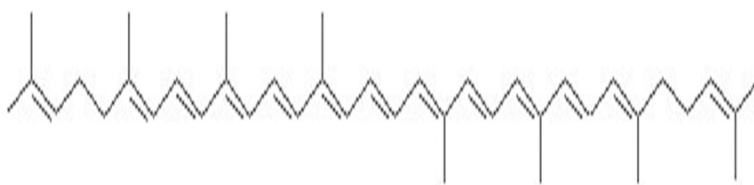
synthase and the production of prostaglandin E2 and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) [42].

#### *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, connexin [26, 47]. Phosphorylation/dephosphorylation of functional connexin 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-hydroxybutyl) 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 astax-

anthin 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- $\kappa$ B), COX-2, matrix metalloproteinases (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 peroxy 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-

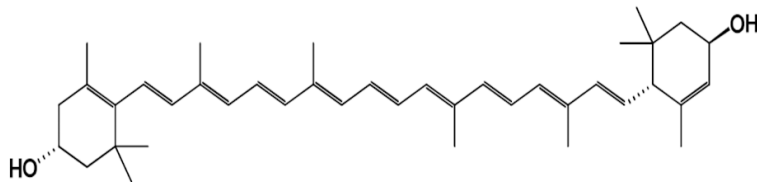
ylglutaryl-coenzyme A reductase enzyme [71]. Agarwal and Rao [67] documented that the singlet quenching ability of lycopene is twice as powerful as that of beta-carotene and 10 times higher than that of alpha-tocopherol. Earlier in this relation Fuhrman et al. [71] showed in six

healthy male subjects given a dietary supplementing 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 peroxy 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  $\alpha$  and  $\beta$ -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  $\alpha$  and  $\beta$ -carotenes (at a moderate dose) increased gap-junctional intercellular communication [22]. One study showed combination of lycopene and  $\beta$ -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 PPAR $\gamma$ -LXR $\alpha$ -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<sub>40</sub>H<sub>56</sub>O<sub>2</sub>. 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

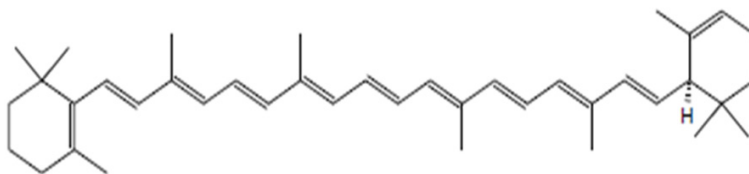
Lutein is especially concentrated in leafy green vegetables, many fruits, and colored vegeta-

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].

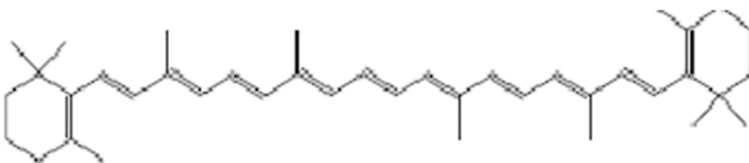
### *Anti-cancer activity*

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 pre-neoplastic 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 chemoprotective 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  $\alpha$ -carotene.



**Figure 5.** Molecular structure of  $\beta$ -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].

#### $\alpha$ -carotene

##### Structure

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

##### Function

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

ed the protective effects of  $\alpha$ -carotene on preneoplastic colorectal adenocarcinoma lesions.

##### Anti-cancer activity

Animal studies have shown that the  $\alpha$ -carotene has higher activity than  $\beta$ -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  $\alpha$ -carotene was by 25%. The average multiplicity (number of tumors/mouse) of tumors in the positive control group was 3.73/mouse, while the  $\alpha$ -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  $\alpha$ -carotene-treated group had 1.33/mouse.

#### $\beta$ -carotene

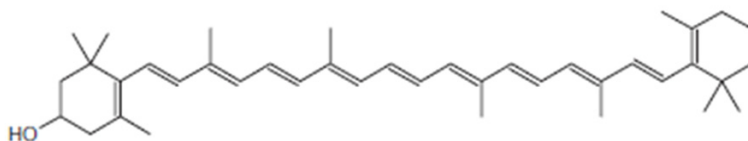
##### Structure

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

##### Function

The  $\beta$ -carotene found in green leafy vegetables, orange, yellow fruits and vegetables.  $\beta$ -carotene can be converted to vitamin A in humans.  $\beta$ -Carotene and its oxidative metabolite, apo-14'-carotenoic acid, are shown to invert the down-regulation of RAR $\beta$  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 anti-oxidant, 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 prod-

ucts 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. salina* micro-alga has anti-cancer activity.

## β-cryptoxanthin

### Structure

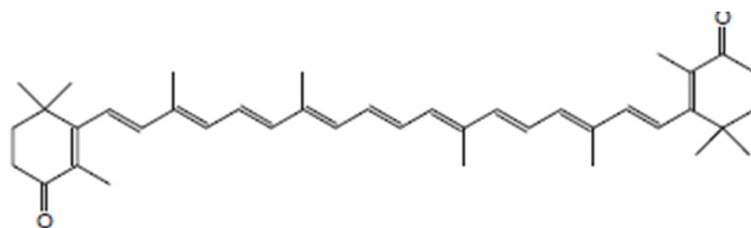
The β-cryptoxanthin is hydrocarbon carotenoid that is cyclized. The molecular structure of α-carotene is presented in **Figure 6**.

### 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  $\beta$ -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  $\beta$ -cryptoxanthin and fiber prevents colitis and obesity-related colon tumorigenesis [149, 151]. Serum levels of  $\beta$ -cryptoxanthin have been inversely associated with the occurrence of human cervical cancer [152]. In addition, the dietary consumption of  $\beta$ -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  $\beta$ -cryptoxanthin. In addition, there are other reports documenting the efficiency of  $\beta$ -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

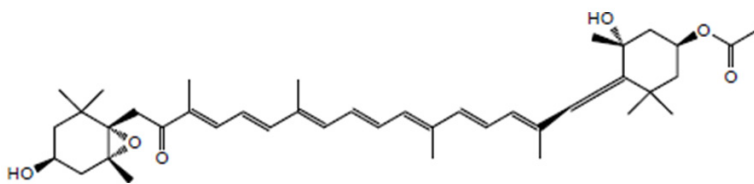
Canthaxanthin for first time was isolated from the edible mushroom, *Cantharellus cinnabarinus*. Also, it is found at the end of the growth phase in several green algae, blue-green algae, or in addition to, primary carotenoids. It has in bacteria, crustacea and various species of fish including carp (*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  $\beta$ -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**.

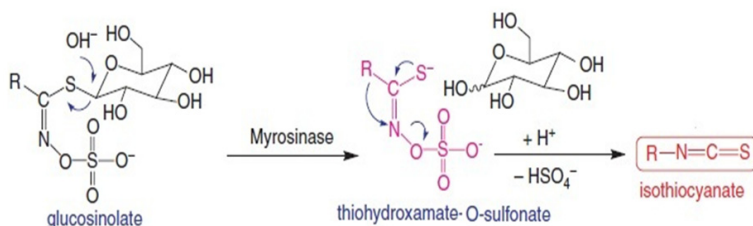
#### Function

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  $\alpha$ ,  $\delta$  and  $\epsilon$ ), 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 PPAR $\gamma$  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 (NRF2)/antioxidant response element (ARE) pathway, anti-inflammatory activity by prevention of nuclear factor kappa B (NFkB), 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- $\kappa$ B-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  $\mu\text{M}$  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  $\mu\text{M}$ ) 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  $^{14}\text{C}$ -sulforaphane and  $^{14}\text{C}$ -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  $\mu\text{mol}$  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 ER $\alpha$  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 LTP-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, glucosomodulatory 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  $\beta$ -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* ( $4 \times 10^8$  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 pan-

creatic 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 5 $\alpha$ reductase, 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 pre-paid 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.

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### 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

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