Abstract

Reactive oxygen species (ROS) and oxidative damage to biomolecules have been postulated to be involved in the causation and progression of several chronic diseases, including cancer and cardiovascular diseases, the two major causes of morbidity and mortality in Western world. Consequently dietary antioxidants, which inactivate ROS and provide protection from oxidative damage are being considered as important preventive strategic molecules. Carotenoids have been implicated as important dietary nutrients having antioxidant potential, being involved in the scavenging of two of the ROS, singlet molecular oxygen (\(1^{O}_2\)) and peroxyl radicals generated in the process of lipid peroxidation. Carotenoids are lipophilic molecules which tend to accumulate in lipophilic compartments like membranes or lipoproteins. Chronic ethanol consumption significantly increases hydrogen peroxide and decreases mitochondrial glutathione (GSH) in cells overexpressing CYP2E1. The depletion of mitochondrial GSH and the rise of hydrogen peroxide are responsible for the ethanol-induced apoptosis. Increased intake of lycopene, a major carotenoid in tomatoes, consumed as the all-trans-isomer attenuates alcohol induced apoptosis in 2E1 cells and reduces risk of prostate, lung and digestive cancers. Cancer-preventive activities of carotenoids have been associated as well as with their antioxidant properties and the induction and stimulation of intercellular communication via gap junctions which play a role in the regulation of cell growth, differentiation and apoptosis. Gap junctional communication between cells which may be a basis for protection against cancer development is independent of the antioxidant property.

Keywords: Tetraterpenes; Carotenoids; Lycopene; Antioxidants; Cardiovascular; Cancers

1. Introduction

Carotenoids belong to the tetraterpenes family and are represented by more than 600 known natural structural variants. Carotenoids are synthesized in plants, fungi, bacteria and algae whereas in animals and human they are not and are incorporated from their diet. The formation of the tetraterpene skeleton (phytoene), results from a loss of a proton, generating a double bond in the center of the molecule. Carotenoids are divided in two classes, carotenes containing only carbon and hydrogen atoms and oxocarotenoids (xanthophylls) which carry at least one oxygen atom. According to the number of double bonds, several cis/trans (E/Z) configurations are possible for a given molecule. In bacteria the double bond has trans-configuration whereas in plants and fungi this double bond has the cis-configuration and an additional isomerization step is involved to change the configuration of the central double bond giving eventually lycopene.

Fig. 1. In plants and fungi, the central double bond of phytoene has the cis-configuration and an isomerization step is involved to change the central double bond to trans configuration which is subsequently metabolized to lycopene.

Lycopene is an open chain hydrocarbon containing 11 conjugated and 2 non-conjugated double bonds arranged in a linear array (Fig. 1). During chemical reactions, light or thermoenergy, these bonds can undergo isomerization from trans to mono or poly-cis isomers and the most commonly identified are all trans, 5-cis, 9-cis, 13-cis and 15-cis isomeric forms of lycopene. \(\alpha\)-Carotene has a \(\beta\)-ring at one end of the chain and an \(\varepsilon\)-type at the other. \(\gamma\)-Carotene, a precur-
sor of β-carotene and δ-carotene, a precursor of α-carotene are carotenoids where only one end of the chain has become cyclized (Fig. 2). Xanthophylls, oxygenated, green leaf carotenoids such as zeaxanthin, lutein and violaxanthin are also widely distributed (Fig. 3). Carotenoids are natural pigments contributing to yellow, orange (yellow and orange fruits and vegetables contain hydrocarbon carotenes with substantial levels of cryptoxanthins and xanthophylls) and red pigmentation to plant tissues (red fruits and vegetables contain mainly lycopene). The green vegetables had high contents of both xanthophylls and hydrocarbon carotenes. Lycopene is a characteristic lipophilic red pigment in ripe tomato fruit (Lycopersicon esculentum; Solanaceae). Since it lacks β-ionone ring structure, it lacks provitamin A activity. The orange color of carrots (Daucus carota; Umbelliferae/Apiaceae) is caused by β-carotene, widespread in higher plants and the brilliant red pigment of pepper (Capsicum annuum; Solanaceae) is due to capsanthine. Astaxanthine, is commonly found in marine animals and is responsible for the pink/red coloration of crustaceans. Shellfish and fish such as salmon are unable to synthesize carotenoids; hence, astaxanthin is produced by modification of plant carotenoids obtained in the diet. Carotenoids function along with chlorophylls in photosynthesis and serve as important protectants for plants and algae against photooxidative damage, quenching toxic oxygen species. Some herbicides (bleaching herbicides) act by inhibiting carotenoids biosynthesis and the unprotected plant is subsequently killed by photooxidation.

In animals and human, carotenoids particularly β-carotene and lycopene, play a role in the protection against photooxidative processes by acting as singlet molecular oxygen and peroxyl radicals scavengers and can interact synergistically with other antioxidants. They have been implicated in the inhibition of cancer cells in vitro [1–3], in animal models [4–8] and in human, as important dietary phytonutrients having cancer preventive activity for lung, colon, breast and prostate cancer [9–11].

The A group of vitamins are important metabolites of carotenoids. Vitamin A1 (retinol) has a diterpene structure but it is derived in mammals by oxidative metabolism of tetraterpenoid, mainly β-carotene, taken in the diet. Cleavage occurs in the mucosal cells of the intestine and is catalysed by an O2-dependent dioxygenase, probably via an intermediate peroxide. Vitamin A2 (dehydroretinol) is an analog of retinol containing a cyclohexadiene ring system. Retinol and its derivatives are found only in animal products and these provide some of our dietary need (Fig. 4).

2. Bioavailability of carotenoids

Among the 600 known carotenoids in nature, only about 20 are found in human plasma and tissues. Lycopene is the most predominant carotenoid in human plasma and has a half life of about 2–3 days. Owing to its lipophilic nature, lycopene was found to concentrate in LDL and VLDL fractions and not in HDL fraction of the serum [29]. The strong association with plasma cholesterol is most likely due to the fact that lycopene is predominantly transported in LDL which carries the bulk of cholesterol in the plasma [30–32]. Lycopene is a non-provitamin A and one of the major carotenoids in western diets accounting for more than 50% of
but isomerization to trans occurs during cooking, food processing or storage [13,14]. 

Fig. 4. Vitamin A$_1$ (retinol) is derived in mammals by oxidative metabolism of β-carotene, taken in the diet. Cleavage is catalysed by an O$_2$-dependent dioxygenase, probably via an intermediate peroxide. Vitamin A$_2$ (dehydro-retinol) is an analog of retinol containing a cyclohexadiene ring system. Retinol and its derivatives are found only in animal products.

carotenoids in human serum [12]. Tomato products (juice, ketchup, soup, sauce) are the major contributors of lycopene carotenoids in human serum [12]. Other sources rich in lycopene include watermelon, pink grapefruit, pink guava and papaya [20,21]. Lycopene is synthesized via a series of four desaturation steps. tomato plant tissues, all-trans is the predominant isomeric form of lycopene but isomerization to cis occurs during cooking, food processing or storage [13,14]. trans-lycopene is cyclized to β-carotene and trans-β-carotene were stable for up to 3 years of storage in liquid frozen serum at –80 °C [15]. Consumption of tomato products with olive oil but not with sunflower oil improves the antioxidant activity of the plasma [19]. Other sources rich in lycopene include watermelon, pink grapefruit, pink guava and papaya [20,21]. Lycopene is synthesized via a series of four desaturation reactions from phytene. These reactions occur in the plastids of higher plants and are catalyzed by two membrane bound desaturases [22]. Lycopene itself is cyclized to x and β-carotenoids both of which are precursors of xanthophylls, found in the photosynthetic apparatus. The genes for virtually all these enzymes have been cloned and can now be used for plant transformations, particularly to elevate the level of lycopene in tomatoes [23].

Animals maintained on lycopene diet, consumed on average 142 µg of lycopene per day of which 104 µg was absorbed by the body (which corresponds to 73% net dietary uptake) calculated as the difference between lycopene intake and fecal output [24]. Ingested carotenoids including lycopene are incorporated into dietary lipid micelles, absorbed into the intestinal mucosal lining via passive diffusion. They are incorporated into chylomicrons and released into lymphatic system for transport to the liver. Lycopene accumulates in hepatocytes and to a lesser extent in spleen. It tends to accumulate in tissues such as testes, adrenal glands and prostate [25] Carotenoids are transported by the lipoproteins into the plasma for distribution to different organs [26–28].

Although trans-lycopene constitutes the predominant isomer in food sources, in human plasma, 50% of the total lycopene has been found as cis isomers [25]. Whether this is due to in vivo isomerization or preferential absorption of cis-lycopene is still unclear. Very little is known about in vivo metabolism of lycopene. A number of oxygenated metabolites have been found in plasma and tissues such as 2,6-cycloxylycopene-1,5-diols [33]. It can undergo in-vivo oxidation to form epoxides that can be converted to 5,6-dihydroxy-5,6-dihydrolycopene [34]. These oxygenated lycopenes are products of in vivo oxidation and may have physiological roles per se.

Carotenoids are lipophilic molecules which tend to accumulate in lipophilic compartments, like membranes or lipoproteins. They are often solubilized in organic solvents such as tetrahydrofuran (THF) or dimethylsulfoxide (DMSO). However, an uncontrolled precipitation process occurs upon addition of these solutions to aqueous media. In this process, carotenoid crystals are formed with a non-controllable particle size. The solubility and uptake of these large crystals in the cells is quite limited and there is almost no protection against chemical degradation. Alternative ways of delivering lipid-soluble compounds include micelles, microemulsions, nanoparticles, water-dispersible beadlets, artificial liposomes, or specialized formulations, each of which has an influence on the uptake and stability of the compound [35–38]. Synthetic lycopene is a red crystalline powder that is soluble in fat and most organic solvents, but insoluble in water. It is sensitive to light and oxygen and is not suitable for commercial use. The market material contains 5–10% lycopene in beadlet formulations [39]. It has a low order of acute toxicity and no teratogenic effects were noted in rats with 1000 mg/kg body weight/day. The high concentration of lycopene in blood correlates with reduced risk of prostate cancer [40–43], digestive tract cancers [44–46], pancreatic cancer [47] cervical intraepithelial neoplasia [48] and myocardial infarction [17,49]. It is assumed that these effects are associated to its high antioxidant activity and singlet oxygen quenching capacity [29]. In addition, lycopene levels are shown to be inversely associated with age [50,51]. Blood lycopene level may differ from blood β-carotene level. In smokers and in alcohol consumers the blood level of β-carotene is lower than that of non-smokers [52–55,57] which does not seem to be the case for lycopene [50,51,56,57].

3. Cellular and molecular processes

3.1. The carotenoid antioxidative effects

Oxidative stress has been widely postulated to be involved in the causation and progression of several chronic diseases. ROS are generated endogenously through normal metabolic activity, life style activities, and diet. They react with critical cellular biomolecules such as lipids, proteins and DNA and initiate events that lead to increased risk of chronic disease such as cancer, cardiovascular disease, and osteoporosis. Consequently, dietary antioxidants which inactivate ROS
and provide protection from oxidative damage are being considered as important preventive strategic molecules [58–63]. The total antioxidant capacity of plasma is due to the relative concentration in antioxidant compounds and to their synergism. In particular an interaction exists between aqueous and lipophilic antioxidants in defending lipoproteins against oxidative damage [64, 65]. Carotenoids are most likely involved in the scavenging of two ROS, singlet molecular oxygen (1O2) and peroxyl radicals. They are also effective deactivators of electronically excited sensitizer molecules which are involved in the generation of radicals and singlet oxygen [66]. Dietary carotenoids protect human lymphocytes from damage by singlet oxygen 1O2, and lower the risk for several degenerative disorders, including various tissues belong to the group of highly active quenchers of 1O2. The most efficient carotenoid is the open ring carotenoid lycopene, which contributes up to 30% to total carotenoids in humans [67–70]. Scavenging of peroxyl radicals generated in the process of lipid peroxidation interrupts the reaction sequence which finally leads to damage in lipophilic compartments. Moreover, induction of phase II enzymes, conjugate reactive electrophiles and act as indirect antioxidants, achieving protection against a variety of carcinogens in animals and humans. Transcriptional control of the expression of these enzymes is mediated at least in part through antioxidant responsive elements (ARE). The transcription factor Nrf2, which binds to ARE, appears to be essential for the induction of glutathione-S-transferases (GSTs), NAD(P)H:quinone oxidoreductase (NQO1) as well as the thiol-containing reducing factor, thioredoxin [71, 72]. In rodents, lycopene resulted in increased levels of GSH and the phase II GSTs [73, 74]. Canthaxanthin and astaxanthin (not lutein and lycopene) were active in inducing phase II metabolizing enzymes, p-nitrophenol-UDP-glucuronosyl transferase and NQO1 [73, 74]. Lycopene was reported to be more effective than β-carotene in cell protection against hydrogen peroxide (H2O2) and nitrogen dioxide radical (NO2) components that can arise from cigarette smoke [75–79]. Clinical trials on the incidence and mortality of cancer and cardiovascular disease in smokers have shown that β-carotene supplemental is either non-protective or even detrimental [80, 81]. One of the reasons for this is that the antioxidant activity of carotenoids depends on the oxygen tension present in the system. At low partial pressures of oxygen such as those found in most tissues under physiological conditions, β-carotene was found to inhibit oxidation. The initial antioxidant activity of β-carotene is followed by a prooxidant action at high oxygen tension. Thus, in thymocytes, β-carotene is an antioxidant at low oxygen pressure but a pro-oxidant at high oxygen concentrations [82]. In addition, lycopene may have also prooxidant activities depending on the type of oxidants used. Thus, it can be either antioxidant or prooxidant at normal oxygen tension in human foreskin fibroblasts cells (Hs68) [83]. The prooxidant effects of β-carotene may be related to adverse effects observed under the supplementation of high doses of β-carotene [84, 85]. However, it has been suggested that some of the degradation products of β-carotene rather than β-carotene itself may be prooxidant or procarcinogenic [86, 87]. Cu(II)-initiated LDL oxidation was inhibited in purified LDL by β-carotene but not by lycopene or lutein [88]. Furthermore, in vitro enrichment of LDL with β-carotene inhibited endothelial cell-mediated oxidation, while enrichment with lycopene or lutein enhanced cell-mediated oxidation [90]. In liposomes oxidized by peroxyl radicals, the ineffectiveness of lycopene was probably due to the rapid degradation of β-carotene [89]. However, it remains unclear how β-carotene and lycopene may enhance lipid peroxidation. In smokers it has been suggested that β-carotene forms radical cations by regenerating a vitamin E radical [91, 92]. Vitamin C plays an important role in reducing the radical cation of β-carotene [91, 92], however, because the high lipophilicity of β-carotene and its location at the interior membrane, the hydrophobic vitamin C cannot efficiently reduce the carotene radicals. Another possibility is that β-carotene may react with lipid peroxyl radicals and form radical cations, which can then be reduced by vitamin E. Vitamin C in turn can reduce vitamin E radical to regenerate vitamin E to prevent the damaging effects of β-carotene cation [93]. Analysis of the antioxidant status of blood in rats, revealed that some antioxidant enzymes, such as superoxide dismutase, glutathione reductase and glutathione peroxidase can be induced by lycopene [94]. Recently, it has been reported that lycopene prevents cataractogenesis in vivo and in vitro by virtue of its antioxidant properties [95].

4. Effect on gap junctional communication

Gap junctions are cell-to-cell channels which enable connecting cells to exchange low-molecular weight compounds like nutrients and signaling molecules [96]. One feature of carcinogenesis is the loss of gap junctional communication (GJC) [97]. Induction of intercellular communication via gap junctions can be achieved with carotenoids and retinoids and is correlated with inhibited cell growth of chemically transformed cells [98]. Non-tumorous cells communicate via GJC, whereas most tumor cells have dysfunctional homologous or heterologous GJC [99]. Carotenoids, in addition to their antioxidant properties, stimulate GJC in a differential and dose dependent manner [100–102]. Stimulatory effects on GJC were described for lycopene which also affects cell growth [100–103]. The biochemical mechanism underlying the activation of GJC is not yet well understood. Carotenoids have been reported to react with almost any radical species.
The products of such reactions are frequently short-lived radical species. In the majority of interactions with radicals, carotenoids break down to degradation products similar to what is seen with oxidative degradation [104]. There is evidence from cell culture studies that central cleavage products of carotenoids are ultimately active components triggering GJC. Oxidation products such as the dialdehyde 2,7,11-trimethyl-tetradecahexaene-1,14-dial obtained from the oxidation of lycopene, stimulates GJC in WB-F344 cells, rat liver epithelial cells [104] but other oxidation products formed upon chemical oxidation of lycopene were not active. Lycopene increases GJC between cells and enhances the expression of connexin 43, a gene encoding major gap junction protein, and thereby upregulated GJC and acts as anti-carcinogen. However, its effect is less pronounced than β-carotene or canthaxanthin [105–107]. Other mechanisms including posttranslational modification, protein trafficking or changes in pH or calcium levels may be also relevant in the stimulation of GJC [108–110]. Loss of GJC may be important for malignant transformation, and its restoration may reverse the malignant process [99,100]. The GJC ability of lycopene and its singlet oxygen quenching abilities or antioxidant properties are independent of each other (Fig. 5) [101,102].

5. Role of carotenoids in human health

Since carotenoids are highly hydrophobic, their interaction with ROS is expected to occur in a lipophilic environment, such as in cell membranes and lipoprotein components. The carotenoids found in cells and tissues are selectively absorbed by membranes depending on the structural carotenoid features (size, shape and polarity), as well as on membrane characteristics (composition and fluidity) [111]. These properties determine the incorporation yield and the carotenoid’s ability to fit into the membrane bilayer [28]. Controversial data are reported about location and distribution of carotenoids in the membrane bilayers. Specific interactions with membranes can occur in the presence of non-polar carotenoids (β-carotene and lycopene) or polar carotenoids (zeaxanthin and lutein). The antioxidant capacity of these two classes of carotenoids proved to be dependent on their different location in the bilayer. While β-carotene and lycopene were able to quench radicals in the hydrophobic part of the membrane, zeaxanthin was effective as an antioxidant in the polar region, exposed to an aqueous environment. Polar carotenoids can regulate the membrane fluidity in a way similar to cholesterol, although they locate differently within the lipid bilayer membrane [112–114].

6. Lycopene effects in alcohol-induced liver injury

Oxidative stress has been implicated in the pathogenesis of alcohol-induced liver injury [115]. Induction of cytochrome P4502E1 (CYP2E1) by ethanol is one of the main mechanisms through which ethanol generate oxidative stress [116]. Several pathways have been shown to contribute to the pathogenesis of alcoholic liver disease [117]. One of these is the induction of CYP2E1 by ethanol with the generation of oxidative stress and lipid peroxidation upon oxidation of ethanol [118]. When rats were fed ethanol with diets containing polyunsaturated fatty acid (PUFA), this toxicity is increased possibly because the presence of PUFA and enhanced lipid peroxidation after induction of CYP2E1 by ethanol [119]. Oxidative stress generated in the HepG2 human hepatic cells transfected with CYP2E1 cDNA (2E1 cells), increased H₂O₂ production that is associated with depletion of mitochondrial GSH are responsible for the ethanol induced apoptosis. In 2E1 cells that kept some liver characteristics, without expressing cytochrome P450 activity, lycopene significantly attenuates alcohol-induced apoptosis [120]. Moreover, arachidonic acid (AA), is an important constituent of membrane phospholipids. The double bonds found in AA of the cellular lipids are available targets for ROS. After conversion to prostaglandins (PG) leukotrienes and generation of oxygen-derived free radicals, it mediates a variety of pathological processes [121–123]. Because of the oxidative stress, AA is toxic to HepG2 and 2E1 cells. Although, lycopene at 10 µM attenuated AA toxicity in HepG2, the most significant effect was observed in 2E1 cells, suggesting that lycopene acts as an anti-oxidant thereby preventing the severe oxidative stress induced by AA in 2E1 cells [124].
7. Photoprotective potential of carotenoids

Photooxidative processes play a role in the pathobiocchemistry of light exposed tissues including the eye and the skin. Age-related macular degeneration which affects the macula lutea of the retina, the area of maximal visual acuity is a major cause for irreversible blindness among the elderly in the Western world [125]. Macular pigments protect against the photooxidative processes which may be related to the antioxidant activities of the macular carotenoids and/or to their light filtering effects [126]. While lutein and zeaxanthin are responsible for coloration of the macula lutea, lycopene, \( \alpha \)-carotene or \( \beta \)-carotene are not found in this tissue.

Ultraviolet (UV) irradiation is associated with oxidative processes involved in photoaging, which induce photodamage and lead to premature skin aging [127]. Following UV irradiation, a cascade of genes are induced, including metalloproteinase 1 (MMP-1) [128] and heme oxygenase 1 (HO-1) [129,130], respectively, the interstitial collagenase and the oxidative stress marker gene. Singlet oxygen is strongly implicated in the induction of these two genes [131,132]. The physiological consequence of increased MMP-1 expression is increased skin collagen degradation and subsequent formation of wrinkles [127,133]. Protection against MMP-1 UV-induction is obtained with low concentrations of vitamin C, vitamin E or carnosic acid. In contrast, \( \beta \)-carotene or lycopene stimulated MMP-1 expression. This effect was completely suppressed when vitamin E was included in a nanoparticle formulation [134]. Thus, depending on the experimental conditions, such as oxygen tension, carotenoid concentration and interactions with other antioxidants influencing the cellular and molecular responses, \( \beta \)-carotene and lycopene can act as antioxidants or prooxidants [135,136]. HO-1, a general stress gene is induced following UVA radiation and is highly implicated in skin aging [129,130]. UV-induced HO-1 mRNA expression was not affected by vitamin C, vitamin E or carnosic acid at the same concentrations that were effective for inhibition of MMP-1 expression. HO-1 expression was stimulated by \( \beta \)-carotene when given alone, but the combination of \( \beta \)-carotene, vitamin C and vitamin E suppressed this induction. Physiologically HO-1 represents an early response to environmental and chemical stress. Thus, although HO-1 mRNA induction indicates higher oxidative stress, it is not clear whether its expression should be stimulated or inhibited.

While topical application of sunscreen provides a barrier protection to the skin epithelium, protection of the more profound dermal layers may be offered by dietary antioxidants [137]. Protection by \( \beta \)-carotene is enhanced when combined with vitamin E [138]. Ingestion of tomato paste daily for 10 weeks, protected against UV light-induced erythema on the dorsal skin [139]. Lycopene present in skin can act as antioxidant, protecting against UV radiation. However, it is quickly depleted from skin upon exposure to solar radiation [140] and undergoes oxidative or enzymatic cleavage to form apo-carotenoids [141]. Therefore, it has been suggested that lycopene should be delivered as powdered nanoparticles together with vitamin C and or vitamin E [134].

8. Carotenoids and cancer

Before malignancy detection, high blood levels of insulin-like growth factor (IGF-1) predicts an increased risk of breast, prostate, colo-rectal and lung cancers [142–145]. In mammary cancer cells, lycopene treatment markedly reduced IGF-1 stimulation of both tyrosine phosphorylation of insulin receptor substrate and DNA binding capacity of the AP-1 transcription factor [146]. These effects were associated with an increase in membrane-associated IGF-binding proteins (IGFBPs). Moreover, lycopene induced delay in progression through G1 and S phases [3,146]. A similar effect was demonstrated with \( \alpha \)-carotene in GOTO human neuroblastoma cells [147] without apoptotic or necrotic cell death. Cell cycle transition through a late G1 is governed by a retinoblasma protein pathway (pRB) [148], a tumor suppressor that prevents premature G1/S transition via physical interaction with transcription factors of the E2F family. The activity of pRB is regulated by an assembly of cyclins, cyclin dependent kinases (Cdks) and Cdk inhibitors. Cdk activity is modulated in both a positive and a negative manner by cyclins and Cdk inhibitors respectively. The D-type cyclins are the main elements acting as growth factor sensors [149]. Cyclin D1 is an oncogene expressed in many breast cancer cells as well as in primary tumors [150].

The anticancer activity of carotenoid derivatives is mediated by the activation of retinoid receptors [151]. However, it can also be mediated by several cleavage products of \( \beta \)-carotene [152] and lycopene [146]. Lycopene was shown to be a powerful inhibitor of endometrial, mammary (MCF-7) and lung (NCI-H226) human cancer cells proliferation and suppress insulin-like growth factor-I-stimulated growth [153]. Moreover, it inhibits growth and development of KB-1 human oral tumor cells [154] and C-6 glioma cells transplanted into rats [155].

An early epidemiological study on elderly Americans indicated that high intake of tomatoes was associated with a significant reduction of mortality from cancers. The estimated intakes of total carotenoid, \( \beta \)-carotene, \( \alpha \)-carotene, lutein and \( \beta \)-cryptoxanthin were not associated with the risk factor. Higher estimated lycopene intake was inversely related to risk of prostate cancer [156]. Among all dietary carotenoid intake and serum carotenoid concentrations, only lycopene showed an inverse association with the risk of cervical intraepithelial neoplasia as compared to control [157]. Serum lycopene levels were also found to be inversely related to the risk of bladder cancer [158], and breast cancer [159]. Lower serum lycopene levels were also reported in human immunodeficiency virus (HIV) positive women and
children [160, 161]. An inverse relationship between dietary intake of lycopene-rich food and the risk of prostate cancer has been reported while β-carotene, α-carotene, lutein and β-cryptoxanthin did not show the same correlation [156]. However, lycopene alone is not a potent inhibitor of prostate carcinoma cell proliferation. The simultaneous addition of lycopene together with α-tocopherol, at physiological concentrations (less than 1 µM and 50 µM, respectively) resulted in a strong inhibitory effect of prostate carcinoma cell proliferation. The effect of lycopene with α-tocopherol was synergistic and was not shared by β-tocopherol, ascorbic acid and probucol [2].

9. Carotenoids in the prevention of cardio-vascular diseases

Coronary heart disease is the major cause of morbidity and mortality in the Western world. There is extensive evidence that oxidatively modified low-density lipoproteins (LDL) are involved in the initiation and promotion of atherosclerosis [61]. Cigarette smoking is a well-known risk factor for coronary atherosclerosis [162]. Atherogenesis may be due to foam cell production by the introduction of a source of free radicals that cause LDL oxidation [163]. Thus, protection from LDL oxidation by antioxidants may lead to protection against human coronary heart disease. Smokers have significantly lower blood levels of β-carotene than non-smokers [50–55, 164], this does not seem to be the case for lycopene [56, 57, 164, 165]. Since β-carotene and lycopene are transported primarily in LDL, it has been suggested that they are in prime position to protect LDL from oxidation [166]. In a multicenter-case-control study of antioxidant nutrients in adipose tissue and risk of myocardial infarction, it was concluded that lycopene and not β-carotene contribute to the protective effect. The protective potential of lycopene was maximum among individuals with highest polyunsaturated fat stores [49, 167].

In conclusion, the beneficial effects of carotenoids in human disease prevention have been widely reported particularly in alcoholic liver injury, cancer, cardiovascular diseases or as photoprotective. However, it remains to identify and characterize the active carotenoid derivatives and to determine whether this potential is due to a synergistic action of various carotenoids and antioxidant micronutrients.

References


