REVIEW ARTICLE

Carotenoids: potential allies of cardiovascular health?

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Abstract

Carotenoids are a class of natural, fat-soluble pigments found principally in plants. They have potential antioxidant biological properties because of their chemical structure and interaction with biological membranes. Epidemiologic studies supported the hypothesis that antioxidants could be used as an inexpensive means of both primary and secondary cardiovascular disease (CVD) prevention. In fact, the oxidation of low-density lipoproteins (LDL) in the vessels plays a key role in the development of atherosclerotic lesions. The resistance of LDL to oxidation is increased by high dietary antioxidant intake, so that carotenoids, as part of food patterns such as the Mediterranean diet, may have beneficial effects on cardiovascular health too. Further properties of carotenoids leading to a potential reduction of cardiovascular risk are represented by lowering of blood pressure, reduction of pro-inflammatory cytokines and markers of inflammation (such as C-reactive protein), and improvement of insulin sensitivity in muscle, liver, and adipose tissues. In addition, recent nutrigenomics studies have focused on the exceptional ability of carotenoids in modulating the expression of specific genes involved in cell metabolism. The aim of this review is to focus attention to this effect of some carotenoids to prevent CVD.

Keywords: carotenoids; cardiovascular; lycopene; astaxanthin; zeaxanthin; lutein; fucoxanthin; beta-cryptoxanthin; lycopene

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Astaxanthin

Astaxanthin is a red soluble pigment belonging to the family of xanthophylls, abundant in the marine world, where it can be found in microalgae, plankton, krill, fish, and other seafood. It is responsible for the typical coloration of salmon and crustaceans (9). Humans are not able to synthesize astaxanthin and need to take it from food. Once introduced, the duodenum absorbs it, and it passes into the blood, reaches the liver, where it binds to lipoproteins before being distributed throughout the whole body. Through its high lipophilicity, it can also cross the blood–brain barrier and reach the brain and eye structures. Astaxanthin cannot be converted to vitamin A, which means that excess intake will not cause hypervitaminosis A toxicity (9, 10). In 1987, the United States Food and Drug Administration approved astaxanthin as a feed additive for use in the aquaculture industry and in 1999 it was approved as a nutraceutical human dietary supplement. The microalgae Haematococcus pluvialis, one of the most important species for its production, is a freshwater species of Chlorophyta that produces the astaxanthin isomer (3S, 3S'), which is the form found in wild salmon. Astaxanthin used in nutritional supplements is usually a mixture of configurational isomers produced by Haematococcus pluvialis (11). Astaxanthin showed potential capacity for protecting the organism against a wide range of diseases, and considerable promising applications in the prevention and treatment of various oxidative stress-related diseases, such as cancers, chronic inflammatory diseases, metabolic syndrome, diabetes, diabetic nephropathy, liver and gastrointestinal diseases, neurodegenerative diseases, and even CVD (12–15), considering that oxidative stress is a pathophysiological process involved in atherosclerotic vascular damage (16). Astaxanthin has a strong antioxidant activity, is a great FRs scavenger and in particular a potent quencher of radical oxygen species (ROS) and nitrogen oxygen species (NOS) (17). Several studies showed that its unique chemical structure makes it more stable within the cell membranes, thus allowing a more efficient antioxidant action. Intracellular FRs are captured by astaxanthin and transferred to the extracellular side where they are inactivated by the action of watersoluble antioxidants such as vitamin C. In this way, it is possible to explain the close synergy between hydrosoluble and liposoluble antioxidants (18). Many works highlight that astaxanthin improves blood lipid profile by reducing LDL-cholesterol (LDL-C) and triglycerides (TG), increasing high-density lipoprotein cholesterol (HDL-C), and decreasing markers of lipid peroxidation (19), inflammation (20, 21), and thrombosis (22). Yoshida et al. (23) demonstrated in a randomized placebo-controlled human study (61 non-obese subjects aged 20–65) that astaxanthin consumption (0, 6, 12, and 18 mg/day for 12 weeks) ameliorates TG and HDL-C in correlation with increased adiponectin in humans. Iwamoto et al. (19) demonstrated a significant inhibition of LDL-C oxidation in 24 healthy volunteers who took doses of astaxanthin (from 1.8 to 21.6 mg/day for 2 weeks). Park et al. (24) studied the effects of dietary supplementation of astaxanthin (0, 2, and 8 mg/day, over 8 weeks) on oxidative stress and inflammation: participants taking 2 mg/day had lower hs-CRP at Week 8: the hs-CRP is considered an important indicator of heart disease. There was also a decrease in DNA damage measured using plasma 8-hydroxy-2’-deoxyguanosine after 4 weeks’ treatment. Another potential benefit to cardiovascular health is the fact that astaxanthin lowers the blood pressure and the risk of heart attack for its modulatory effects on nitric oxide (NO) (25, 26); in fact, Hussein et al. (27) found that oral administration of astaxanthin for 14 days significantly lowered the arterial blood pressure in spontaneously hypertensive rats, and the long-term administration for 5 weeks could also delay the incidence of stroke in spontaneously hypertensive rats (27). Also, Pashow et al. suggested that there might be a potential therapeutic role for astaxanthin in the management of myocardial injury, oxidized LDL, and re-thrombosis after thrombolysis, as well as other cardiac diseases, such as atrial fibrillation (17). However, these short-term benefits in vitro and in animal models are not sufficient to affirm undoubted that carotenoids are clearly beneficial for CVD and other diseases, in particular, if we consider that their supplemental, isolated form in doses much larger than usual in diet have not frequently showed long-term benefits (28) against several null or adverse studies of some carotenoids supplements (29–31).

Fucoxanthin

Fucoxanthin is an orange carotenoid present in edible brown seaweeds, such as Undaria pinnatifida (Wakame), Hizikia fusiformis (Hijiki), Laminaria japonica (Ma-Kombu), and Sargassum fulvellum. It belongs to the class of non-pro-vitamin A carotenoids, and is a xanthophylls, whose distinct structure includes an unusual allenic bond, epoxide group, and conjugated carbonyl group in polyene chain with antioxidant properties (32, 33). Dietary administrated fucoxanthin is converted to amarouciaxanthan A via fucoxanthinol in mice (34, 35). This metabolic conversion, requiring NAD(P)+ as cofactor, was also observed in human hepatoma cell (HepG2) (36). Dietary fucoxanthin is hydrolyzed to fucoxanthinol in the gastrointestinal tract by digestive enzymes such as lipase and cholesterol esterase.
and then converted to amarouciaxanthin A in the liver (37). Thus, these metabolites are considered to be the active forms that exert physiological functions in the body. Amarouciaxanthin A is stored in abdominal white adipose tissue (WAT), fucoxanthinol in other tissues (38). Currently, there are few data about pharmacokinetics of fucoxanthin and its metabolites in human subjects. Recent studies reported that fucoxanthinol was detectable in human plasma after daily intake of Wakame. Data about pharmacokinetics of fucoxanthin demonstrated that bioavailability and metabolism of fucoxanthinol is higher in humans than in mice (39–41), but fucoxanthin absorption rate is generally affected by the composition of food matrix: for example, its solubility in soybean oil and in other vegetable oils is very low, while fucoxanthin can easily dissolve in medium-chain triacylglycerols (MCT) or in fish oil (42). Fucoxanthin acts on the reduction of major cardiovascular risk factors, such as obesity, diabetes, high blood pressure, chronic inflammation, plasma and hepatic triglyceride, and cholesterol concentrations (43–45). The identification of substances that can decrease or prevent obesity remains the main goal of medical research. Adaptive thermogenesis by uncoupling protein-1 (UCP1) could be a physiological defense against obesity (43). UCP1 expression is known to be a significant component of whole body energy expenditure, and its dysfunction contributes to the development of obesity (46). In fact, during normal metabolism, the body produces heat, a process also called thermogenesis, and fucoxanthin increases the amount of energy released as heat in fat tissue. UCP1 induction by fucoxanthin metabolites accumulated in WAT is of great interest because UCP1 is normally expressed only in brown adipose tissue (BAT) and not in WAT. This protein, situated in the mitochondrial inner membrane, dissipates the pH-gradient generated by oxidative phosphorylation, releasing chemical energy as heat. UCP1 expression in WAT by fucoxanthin intake leads to oxidation of fatty acids and heat production in WAT (47). Fucoxanthin was found to induce both protein and mRNA expression of UCP1 in WAT (44). This finding will give a clue for new dietary anti-obesity therapies. All these promising scientific findings have been obtained through animal studies, and therefore the fucoxanthin, to keep its promises of anti-obesity nutraceutical, needs to be extensively tested on humans. Only one study has been conducted in humans, which has evaluated the effectiveness of fucoxanthin supplementation for weight loss. In this study, Abidov et al. (48) tested the fucoxanthin in 151 non-diabetic, obese premenopausal women. Three quarters of participants were affected by non-alcoholic fatty liver disease (NAFLD), while the remaining had a normal liver function. The women were divided into two groups and invited to take respectively 600 mg of Xanthigen, which contains 300 mg pomegranate seed oil (PSO) and 300 mg brown seaweed extract containing 2.4 mg fucoxanthin or a placebo for 16 weeks. The diet was reduced to 1,800 kcal per day and was composed of 50% carbohydrates, 30% protein, and 20% fat. The results provided a significant reduction of body weight, fat, and systolic/diastolic blood pressure; decreased levels of TG and of some enzymes (CRP, glutamic pyruvic transaminase (GPT), glutamic oxaloacetic transaminase (GOT), gamma-glutamyl transpeptidase (gamma-GT)), and significant increase in resting energy expenditure (REE) measured by indirect calorimetry. The 16-week supplementation with 4.0 mg/day fucoxanthin showed an important increase in REE and an even greater increase in the group taking fucoxanthin at a dose of 8 mg. Obese patients with NAFLD commonly present elevated markers of liver inflammation and injury, including CRP, GOT, GPT, and gamma-GT (49). A significant reduction in body weight and fat in obese individuals results in the downregulation of inflammatory markers and prevent metabolic syndrome. It has been demonstrated that increased GPT and CRP plasma levels are associated with decreased hepatic insulin sensitivity, insulin resistance, and an increased risk for the onset of metabolic syndrome and type 2 diabetes. The potential antidiabetic effects of fucoxanthin are attributable to the ability of this molecule to induce weight loss and WAT reduction. The adipocyte has recently been recognized as an endocrine cell for its role in the secretion of biologically active mediators, termed adipokines/chemokines, including leptin, adiponectin, resistin, tumor necrosis factor-alpha (TNF-alpha), and monocyte chemoattractant protein-1 (MCP-1). Some adipokines are reported to alter insulin sensitivity and glucose and lipid metabolism in muscle, liver, and adipose tissues (50). The participation of macrophages in inflammatory responses by the release of pro-inflammatory mediators (TNF-alpha and MCP-1) under obesity conditions has also been reported. The chronic low-grade inflammation elicited by pro-inflammatory mediators in the WAT leads to insulin resistance (51). A recent study, using cultivated cells, showed that fucoxanthinol prevents inflammation and insulin resistance also by inhibiting NO and PGE2 production through the downregulation of inducible nitric oxide synthase (iNOS) and COX-2 mRNA expression as well as adipocytokine production in WAT. iNOS is an enzyme that produces NO, which is a FR molecule related to the pathogenesis of inflammation. The overexpression of iNOS mRNA has been observed in WAT of obese mice and adipocytes (52). An interesting, extra metabolic benefit of fucoxanthin administration in rodents is the promotion of the synthesis of docosahexaenoic acid (DHA) in the liver, resulting in improvements in lipid profile (53). Experiments on stroke-prone spontaneously hypertensive rats (SHRSP) show the possible protective role of fucoxanthin in CVD. Thirty-three male SHRSP rats, 5 weeks of age, were divided into three groups: 1) kaolin group, which was given a normal diet (kaolin is a non-nutrient material); 2) Wakame
(Undaria Pinnatifida) group (normal diet containing Wakame powder); and 3) cellulose group (normal diet containing cellulose). In this study, Wakame delayed the incidence of stroke signs and increased the life span of SHRSPr (54). Clinical research also indicated that the metabolic boost from taking fucoxanthin did not stimulate the central nervous system, meaning it did not cause jitters or loss of sleep such as caffeine, nicotine, or thyroid hormones. So the fucoxanthin may have a potential role in modulation and prevention of human diseases, particularly in reducing the incidence of CVD (55). As a carotenoid, fucoxanthin is a powerful antioxidant that protects cells from FRs damage. A diet rich in fucoxanthin could help to reduce body fat accumulation and to modulate blood glucose and insulin levels, through the regulation of cytokine secretions from WAT. Fucoxanthin proved safe with no side effects, and even provided other health benefits, including improved cardiovascular health, reduction of inflammation (a major cause of heart disease), healthy cholesterol and TG levels, improvements in blood pressure levels, and healthy liver function (56).

Lycopene

Lycopene is the pigment responsible for the red color in some fruits and vegetables, which can be found in high concentration in tomato products, red grapefruits, and watermelons (57–60). It is an unsaturated carotenoid, resulting in an efficient antioxidant, and consumption can prevent both aging and CVD (61–65) because of its important bioactivities. It seems to eliminate ROS, to inhibit lipid peroxidation, and even to reinforce the immune system (57–60). In fact, it is a lipophilic molecule transported in blood by lipoproteins which accumulates in human tissues, also in the vasculature (66). Low plasmatic levels of antioxidant vitamins A, E, beta-carotene, and lycopene were shown to be associated with early carotid atherosclerotic lesions (67). In particular, the Rotterdam Study reported that lycopene was inversely associated with the calcified plaques of the abdominal aorta (62), and several works have clearly associated lycopene with the calcified plaques of the abdominal aorta (62), and several works have clearly associated lycopene with reduced carotid intima-media thickness and lower incidences of cardiovascular accidents, such as CHD and stroke (63). The antiatherogenic effect of lycopene is associated with anti-inflammatory activities, better lipid homeostasis (65) (determining higher serum HDL-C, lower ratio of total cholesterol to HDL, and lower triglycerides), antioxidation and consequent inhibition of LDL peroxidation, and protection of vascular endothelium. In fact, lycopene was shown to decrease vascular oxidative stress and inflammation, blood lipid biomarkers of oxidative stress in vivo (68), and attenuate adhesion molecule expression and interactions between monocytes and endothelial cells (69). This anti-inflammatory effect was realized by inhibiting IL-1 secretion, which is a key factor in inflammatory processes inducing the synthesis of other pro-inflammatory cytokines, adhesion molecules, chemotactic factors, and acute-phase proteins (70, 71). The production of flogistic mediators (such as IL-1, IL-6, and TNF) and the following recruitment of leukocytes to the intima is involved in the early formation of atherosclerotic lesions, conducing to the chronic inflammatory process of atherosclerosis (72). In addition, lycopene displayed positive effects on the maintenance of NO levels, contributing to vasodilatation, even resulting in a more effective slowing of the progression of atherosclerosis than by fluvastatin, thereby reducing the cardiovascular risk (73). These results suggest the beneficial effect of higher serum and tissue levels of lycopene: for this reason dietary intake of lycopene (especially if diet is also rich in extra-virgin olive oil) (74) or lycopene supplementation (75) seems to decrease the risk of CVD (62, 76). However, several factors can affect lycopene bioavailability and absorption: season, dietary sources, food composition, and processing such as cooking or heating (77), which were reported to transform all-trans-lycopene to cis-lycopene (78), which is better absorbed. So higher serum levels of lycopene were found when tomatoes have been consumed cooked rather than raw (79). On the contrary, too much prolonged heat treatment (more than 2 h at 100°C) of tomatoes decreases the total carotenoid content, also affecting the beneficial effects against dyslipidemia and cardiovascular risk (80).

Lutein

Lutein is a pigment (xanthophyll) and a dietary oxygenated carotenoid consisting of 40-carbon hydroxylated compounds found in the human retina in high concentration (81). It is an isomer of the carotenoid zeaxanthin, with identical chemical formulas. Similarly to zeaxanthin, it can just be obtained from supplements or diet, found in several foods, such as yellow corn, egg yolk, orange juice, honeydew melon, and other fruits (82), but especially occurring in dark green vegetables such as turnip greens, kale, parsley, spinach, and broccoli (83). Lutein, which has been shown to prevent lipid peroxidation (84), is well-known to be protective against age-related macular degeneration (AMD) and senile cataract (85, 86), whose major risk factor is oxidative stress (87). In fact, lutein has a strong ROS scavenger capacity (88, 89), blocks the activation of the ubiquitous nuclear transcription factor NF-kB playing a key role in many pathological reactions (90) and the degradation of the inhibitor kB (I-kB) (91). When I-kB is dissociated from the NF-kB complex by lutein, NF-kB can translocate into the nucleus, decreasing inducible gene transcription and synthesis of inflammatory markers such as cytokines, chemokines, and iNOS (92). The final effect of lutein involves not only decreasing the concentrations of TNF-alpha, interleukin 6 (IL-6), prostaglandin 2 (PGE-2), monocyte chemotactic protein 1 (MCP-1), and macrophage inflammatory
protein 2 (MIP-2) (91) but also reducing oxidative stress. However, its antioxidant and anti-inflammatory capacity have been shown to have a positive influence not only on eyes but also in promoting cardiovascular health and decreasing the risk of CAD (93). Recent studies showed that plasmatic lutein and oxidized LDL were inversely correlated, suggesting its potent antioxidant and anti-inflammatory effects also on aortic tissue, which may protect against development of atherosclerosis (94). In fact, several works suggest that in atherosclerosis, serum levels of lutein were significantly lower than that in controls, and that it was inversely associated with carotid stiffness (95). In addition, the ARIC (96) and the CUDAS studies (97) displayed a possible beneficial effect of a lutein-rich diet, and also the Los Angeles Atherosclerosis Study showed the inverse association between plasmatic lutein and atherosclerosis, so that higher levels of lutein (such as zeaxanthin and beta-carotene) may be protective against early atherosclerosis (98, 99). A beneficial effect of lutein on heart and blood vessels was also related to prevention of hypertension. A higher concentration of this carotenoid was generally inversely associated with an increase in systolic blood pressure and incidental hypertension. Subjects with higher lutein levels seem to show lower baseline blood pressure, generally with lower risk for future hypertension, independent of smoking status (100). In addition, lutein seems to exert a cardioprotective effect, bringing therapeutic benefit in the treatment of cardiovascular complications. In fact, FRS and oxidative stress are known to be mediators of myocardial ischemia/reperfusion damage (the restoration of blood flow to ischemic regions, with increased generation of highly reactive oxygen species) (101–103). Lutein protects myocardium from ischemia/reperfusion injury by decreasing oxidative stress and myocytes apoptosis (104). Limiting myocardial injury may prevent contractile dysfunction, reducing morbidity and mortality associated with CAD (105).

Zeaxanthin

Like lutein, zeaxanthin is an oxygenated non-pro-vitamin A carotenoid that consists of a 40-carbon hydroxylated compound (106). Major dietary sources of this xanthophyll in the diet include corn, eggs, orange juice, honeydew melon, and dark green leafy vegetables such as kale, turnip greens, spinach, and broccoli (83). The area of the retina serving central vision is known as the macula lutea because of its yellow coloration from lutein; however, it also contains zeaxanthin. The relative concentration of lutein to zeaxanthin in the macula is distinctive: zeaxanthin is more centralized and lutein predominates toward the outer area of the macula. A xanthophyll-binding protein may explain the differences among people to accumulate these carotenoids into eye tissues. Increased lutein and zeaxanthin intake from both food sources and supplements is positively correlated with increased macular pigment density, which is theorized to lower risk for macular degeneration; in fact, several population studies suggest lower rates of AMD among people with higher levels of zeaxanthin in diet and blood. Possible mechanisms of action for these carotenoids include antioxidant protection of the retinal tissue and the macular pigment filtering of damaging blue light (107). In addition to quenching reactive oxygen species directly, zeaxanthin may prevent protein, lipid, or DNA from oxidative damage by regulating other cellular antioxidant systems. Glutathione is one of the major intracellular antioxidants not only in the lens and plays an important role in protecting cells from oxidative damage (108). In this sense, the protective effects of zeaxanthin, against protein oxidation, lipid peroxidation, and DNA damage resulted to be comparable to α-tocopherol: supplementation with zeaxanthin or α-tocopherol decreases oxidized glutathione (GSSG) and increases the intracellular reduced glutathione (GSH) levels and GSH/GSSG ratio, especially in response to oxidative stress. Thus, zeaxanthin acts as an antioxidant in a directly or indirectly, by regulating glutathione synthesis and therefore glutathione levels. As a consequence, intracellular redox status upon oxidative stress improves and the susceptibility to H₂O₂-induced cell death reduces (82).

Zeaxanthin is not only implied in the health of the eye but also in cardiovascular aspects, such as beta-carotene; zeaxanthin, which resulted inversely correlated with right common carotid artery stiffness; pulse wave velocity; and elastic modulus. The Beijing atherosclerosis study and the Los Angeles Atherosclerosis study also found the inverse association between plasma lutein and early atherosclerosis, and their further studies showed that higher levels of plasma zeaxanthin may be protective against early atherosclerosis (99). These results indicated that zeaxanthin might be beneficial to arterial health.

Beta-cryptoxanthin

Beta-cryptoxanthin is a xanthophylls and one of the lesser-known carotenoids, whose best food sources are oranges, peach, tangerines, and tropical fruits such as papaya. It also has pro-vitamin A activity and seems to have protective health action. Many epidemiological studies showed that dietary beta-cryptoxanthin is associated with improved respiratory function and lower rates of lung cancer: in fact, some prospective studies on dietary intake, lifestyle, and neoplasia identified beta-cryptoxanthin as a protective nutrient (109). In addition, in tissue culture, beta-cryptoxanthin has a direct stimulatory effect on bone formation and an inhibitory effect on bone resorption (110). Epidemiologic studies suggest that the antioxidant potential of dietary carotenoids, such as beta-cryptoxanthin, may protect against the oxidative damage that can result in inflammation. The European Prospective Investigation of Cancer Incidence (EPIC)-Norfolk
study, a population-based prospective study of 25,000 subjects, showed that an increase in beta-cryptoxanthin intake, equivalent to one glass of freshly squeezed orange juice every day, was associated with a reduced risk of developing inflammatory disorders such as inflammatory polyarthritis, which is a synovitis affecting two joint groups, and rheumatoid arthritis (111). The Iowa Women’s Health Study, a large prospective population-based study of 29,000 women aged 55–69 recently reported a protective effect against the development of RA of a high dietary intake of beta-cryptoxanthin but not of beta-carotene, lutein, and zeaxanthin (112): probably the influence of beta-cryptoxanthin on some markers of inflammatory activity may be stronger than those of other carotenoids. It was recently postulated that this role of circulating antioxidants, as scavengers of FRs and inhibitors of oxidative damage leading to the suppression of inflammation, might also have a role in the prevention of CVD. Further epidemiologic studies displayed that CRP and oxidized LDL-cholesterol concentrations, which have also been linked to the development of CVD, are inversely related to serum concentrations of circulating antioxidants, including beta-cryptoxanthin (113). A recent report found that in the general population obesity is negatively related to serum concentrations of beta-cryptoxanthin and positively related to CRP (114). Thus, we could suppose that beta-cryptoxanthin may also be associated with a reduced cardiovascular risk.

**Beta-carotene**

Beta-carotene is one of the most widely studied carotenoids for both its pro-vitamin A activity and its abundance in fruits and vegetables, such as carrot, orange, kale, spinach, turnip greens, apricot, and tomato. It serves as a prehormone that is converted into retinoic acid (RA), which functions as a ligand, regulating the expression of genes involved in metabolic processes (115). Natural beta-carotene comprises several isomers, including all-trans and 9-cis b-carotene. Several epidemiological studies displayed that an abundance of carotenoids in the diet may be protective against many diseases, reducing the risk of CVD and some forms of cancer. In particular, this carotenoid may increase immunological functions by enhancing lymphocyte proliferation and possess antioxidant capacity: the enrichment of LDL with beta-carotene in vitro has been shown to reduce the susceptibility of LDL to oxidative modification (116). Another interesting mechanism to elucidate why carotenoids can prevent CVD is the modulation of vascular NO bioavailability thanks to their reducing activity. In fact, it is well known that one of the earliest pathogenic events in atherosclerosis is represented by the overexpression of cell surface adhesion molecules, which causes the binding of normally non-thrombogenic circulating cells, such as monocytes, to the endothelium: the activation of NF-kB pathway triggers the upregulation of the expression of the vascular cell adhesion molecules (VCAM-1), intercellular cell adhesion molecules (ICAM-1), and E-selectin in response to various inflammatory cytokines (117). NO, constitutively generated by endothelial cells, plays an important role in the maintenance of vascular homeostasis and in the pro-inflammatory response that characterizes the early stages of atherosclerosis: it inhibits the vascular inflammatory response by blocking NF-kB nuclear transfer. A recent study (118) reported that beta-carotene, similar to lycopene, affects NF-kB-dependent expression of adhesion molecule and monocyte–human umbilical vein endothelial cell (HUVEC) interaction induced by TNF-alpha and protect NO bioavailability, thereby reducing TNF-alpha-induced nitro-oxidative stress. In a model of vascular inflammation, the presence of high concentrations of beta-carotene is associated with a significant increase in NO level and bioavailability, as indicated by the increase in cGMP levels: an increased release of NO lead to a downregulation of the expression of NF-kB-dependent adhesion molecules in endothelial cells (119). The maintenance of endothelial NO bioavailability is therefore considered beneficial to endothelial functions and more in general to vascular health. The 9-cis-beta-carotene isomer, present in the highest levels in the alga Dunaliella bardawil, showed positive results too: a recent study demonstrated that combined treatment with the drug bezafibrate and Dunaliella powder enhanced the effect of the fbrate on HDL-cholesterol elevation in human apolipoprotein (120). In fact, the effect of fibrates on HDL levels is suggested to be mediated by its binding to peroxisome-proliferator-activated receptor (PPAR) alpha. Upon ligand binding, PPAR-alpha heterodimerizes with the 9-cis RA receptor (RXR) and this heterodimer regulates gene expression. The hypothesis is that a combined treatment with fbrate and 9-cis-beta-carotene rich powder of the alga Dunaliella bardawil, as a source of 9-cis RA, would improve the drug’s effect on HDL levels (120). Other studies demonstrate that a 9-cis-beta-carotene-rich diet may inhibit atherosclerosis by reducing non-HDL plasma cholesterol concentrations and by inhibiting fatty liver development and inflammation in a mouse model of atherosclerosis (121). Both pathological examination and gene expression showed that a beta-carotene-rich diet reduced inflammation in the livers of mice, by reducing the expression of IL-1a, VCAM-1, and E-selectin. The high-cholesterol diet was shown to induce the expression of several pro-inflammatory genes in the liver and liver inflammation has been suggested to contribute to atherosclerosis; therefore, the reduced levels of these genes in Dunaliella-treated mice can contribute to the protection against diet-induced liver damage and, consequently, atherogenesis. Similar to rexinoids, the 9-cis-rich diet significantly reduced mRNA levels of CYP7a, the rate-limiting enzyme of bile acid synthesis (122) and consequently it may reduce cholesterol absorption in
the intestine. The 9-cis-beta-carotene-rich diet also reduced the expression of other genes involved in cholesterol metabolism, ABCG1, ABCG5, and ABCG8. These transporters are expressed in the liver and play a role in excreting cholesterol and therefore, can be expected to reduce atherogenesis. The beneficial effects on plasma lipids in humans suggest that 9-cis-beta-carotene have the potential to inhibit atherosclerosis progression in humans and probably has the potential to reduce the inflammatory process in general. Also, the Manfredonia Study (whose aim was to assess the relationship between asymptomatic carotid atherosclerosis, as defined by carotid intima-media thickness, and inflammatory markers, plasma lipids, and serum antioxidant vitamins) examined 640 subjects with carotid ultrasound investigation, and the collection of medical history and laboratory data, in order to evaluate beta-carotene effects on the cardiovascular system. Among participants with carotid intima-media thickness ≥0.8 mm, body mass index, blood pressure, total cholesterol, LDL-C, triglycerides, uric acid, CRP, and fibrinogen were significantly higher; concentrations of vitamin A, vitamin E, lycopene, and beta-carotene were lower when compared with participants who did not show evidence of carotid atherosclerosis. This study concluded that the optimal control of hypertension, diabetes, and dyslipidemia, in addition to smoking cessation and an adequate intake of antioxidant micronutrients from foods represent a key for the prevention of atherosclerotic disease (123). Finally, beta-carotene resulted implied even in the control of body fat reserves (124): in mature adipocytes, beta-carotene is metabolized to RA, which decreases the expression of PPAR-alpha and CCAAT/enhancer-binding protein, which are key lipogenic transcription factors. Thus, beta-carotene reduces the lipid content of mature adipocytes. Animal studies indicate that diets low in vitamin A favor adipose tissue formation and enhance formation of intramuscular fat. Regulation of fat reserves by dietary vitamin A can be explained by the metabolism of vitamin A to biologically active retinoid derivatives, which then impact the differentiation and function of adipose tissue. The vitamin A derivative all-trans-RA has been shown to inhibit adipocyte differentiation in cell culture (125). In mature adipocytes, treatment with pharmacological doses of RA can induce lipolysis, mitochondrial uncoupling, and influence the production of adipokines (126) both in cell culture and mouse models. So, a diet rich in beta-carotene and fat directs toward energy expenditure, but in the absence of beta-carotene, adipocytes store energy as fat. In fact, in humans, circulating beta-carotene levels are inversely correlated with risk of type 2 diabetes and obesity (127), which are important cardiovascular risk factors. However, these benefits are associated with dietary consumption and seem to disappear when beta-carotene is administered as a pharmacological supplement, resulting in harmful effects in some subpopulations: administration of synthetic all-trans b-carotene to smokers seems to increase the incidence of lung cancer and CVD (29). In this respect, the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study, conducted in Finland as a joint project between the National Institute for Health and Welfare of Finland and the US National Cancer Institute (NCI), deserve a particular mention: this was a randomized, double-blind, placebo-controlled primary prevention trial to determine whether daily supplementation with alpha-tocopherol, beta-carotene, or both would reduce the incidence of lung or other cancers among male smokers. A total of 29,133 men aged between 50 and 69, who smoked at least five cigarettes per day, were recruited and received either alpha-tocopherol (50 mg/day), beta-carotene (20 mg/day) as all-trans-beta-carotene, both supplements, or placebo capsules for 5–8 years until trial closure; researchers reported that men who took beta-carotene had an 18% increased incidence of lung cancers and an 8% increased overall mortality. Vitamin E had no effect on lung cancer incidence or overall mortality. The men taking both supplements had outcomes similar to those taking beta-carotene alone. The adverse effects of beta-carotene appeared stronger in men with a relatively modest alcohol intake (more than 11 g per day; 15 ml of alcohol is equivalent to one drink) and in those smoking at least 20 cigarettes daily (30). The results of both the trial and post-trial follow-up of the ATBC Study, in conjunction with results from the CARET Study (Beta-Carotene and Retinol Efficacy Trial) which compared the effects of beta-carotene plus vitamin A to placebo in 18,314 men and women aged 45–74 who were either smokers or former smokers, evidenced a 28% higher lung cancer incidence and 17% higher overall mortality in the group taking the vitamin supplementation (31); this continues to support the recommendation that beta-carotene supplementation should be avoided by smokers. In this regard, one of the few studies that showed a long-term benefit of supplemental carotenoids deserve a particular mention: the Age-Related Eye Disease Study (AREDS) is a major clinical trial sponsored by the National Eye Institute, which was designed to learn more about the natural history and risk factors of AMD and cataract and to evaluate the effect of high doses of vitamin C, vitamin E, beta-carotene, and zinc in the progression of AMD and cataract. Results from the AREDS showed that high levels of these antioxidants significantly reduce the risk of advanced AMD and its associated vision loss (28). In May 2013, the NEI completed the Age-Related Eye Disease Study 2 (ARDS2), which tested several changes to the formulation by adding omega-3 fatty acids and by substituting lutein and zeaxanthin for beta-carotene, which prior studies had associated with an increased risk of lung cancer in smokers. The study found that while omega-3 fatty acids had no effect on the formulation, lutein and zeaxanthin together appeared to be a safe and effective alternative to...
beta-carotene. The totality of evidence on beneficial and adverse effects from AREDS2 and other studies suggests that lutein/zeaxanthin could be more appropriate than beta-carotene in the AREDS-type supplements (128). More prolonged follow-up will certainly provide unique and valuable information on the duration of trial effects and potential late effects of intervention with these antioxidant vitamins. Further follow-up will also contribute to our understanding of the biological mechanisms through which such agents affect carcinogenesis and human cancer risk.

**Conclusions**

Pathophysiology of many chronic and acute conditions, especially of CVD, is explained by inflammation and oxidative stress. Apart from sex, age, and genetic factors which cannot be modified, lifestyle and dietary intervention can be considered as new important means of prevention and treatment of cardiovascular risk factors. Whilst it would be beneficial not only to practice regular physical exercise, quit smoking, and reduce sodium and cholesterol (106), a higher dietary introduction or supplementation of antioxidant compounds (55), such as polyphenols, vitamins, and carotenoids would also be beneficial. Numerous evidences confirmed that carotenoids possess antioxidant biological properties due to their chemical structure and interaction with biological membranes. In particular, fucoxanthin, astaxanthin, lycopene, and lutein are strong FRs, quenchers of ROS, and NOS, so that their antioxidant and anti-inflammatory activity may help against cardiovascular risk factors such as markers of inflammation, hyperlipidemia, hypertension, insulin resistance, and obesity. Consequent improvements in blood pressure baseline levels, reduction of inflammation, and correction of dyslipemias can lead to an improvement of cardiovascular health. Further in-depth efforts in this sense could be studied to define a preventive and therapeutic strategy in order to reduce the risk of developing CVD, with promising applications and no side effects.

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**References**

1. Fassett RG, Coombes JS. Astaxanthin: a potential therapeutic agent in cardiovascular disease. Mar Drugs 2011; 3: 447–65.
2. McNulty H, Jacob RF, Mason RP. Biologic activity of carotenoids related to distinct membrane physicochemical interactions. Am J Cardiol 2008; 101: 20–9D.
3. Jackson H, Braun CL, Ernst H. The chemistry of novel xanthophyll carotenoids. Am J Cardiol 2008; 101: 50–7D.
4. Seifried HE, Anderson DE, Fisher EI, Müller JA. A review of the interaction among dietary antioxidants and reactive oxygen species. J Nutr Biochem 2007; 18: 567–79.
5. World Health Organization. Joint WHO/FAO Expert Consultation on Diet, Nutrition and the Prevention of Chronic Diseases. Diet, nutrition, and the prevention of chronic disease. WHO Library Cataloguing-in-Publication Data, WHO Technical Report Series, No. 916. Geneva: 2003.
6. Neaton J, Wentworth D. Serum cholesterol, blood pressure, cigarette smoking, and death from coronary heart disease. Overall findings and difference by age for 316,099 white man. Multiple risk factor intervention trial research group. Arch Intern Med 1992; 152: 36–64.
7. Riccioni G. Carotenoids and cardiovascular disease. Curr Atheroscler Rep 2009; 11: 434–9.
8. Riccioni G, D’Orazio N, Speranza L, Di Ilio E, Glade M, Bucciarelli V, et al. Carotenoids and asymptomatic carotid atherosclerosis. J Biol Regul Homeost Agents 2010; 24: 447–52.
9. Schweigert F. Metabolism of carotenoids in mammals. Basel, Switzerland: Birkhauser Verlag; 1998.
10. Jyonouchi H, Sun S, Tomita Y, Gross MD. Astaxanthin, a carotenoid without vitamin A activity, augments antibody responses in cultures including T-helper cell clones and suboptimal doses of antigen. J Nutr 1995; 125: 2483–92.
11. Guerin M, Huntley ME, Olazola M. Haematococcus astaxanthin: applications for human health and nutrition. Trends Biotechnol 2003; 21: 210–16.
12. Yuan JP, Peng J, Yin K, Wang JH. Potential health-promoting effects of astaxanthin: a high-value carotenoid mostly from microalgae. Mol Nutr Food Res 2011; 55: 150–63.
13. Ellingsen I, Seljelid I, Arnesen H, Tonstad S. Vitamin C consumption is associated with less progression in carotid intima media thickness in elderly men: a 3-year intervention study. Nutr Metab Cardiovasc Dis 2009; 19: 8–14.
14. Carty JL, Bevan R, Waller H, Mistry N, Cooke M, Lunej J, et al. The effects of vitamin C supplementation on protein oxidation in healthy volunteers. Biochem Biophys Res Commun 2000; 273: 729–35.
15. Carpenter KL, Kirkpatrick PJ, Weissberg PL, Challis IR, Dennis IF, Freeman MA, et al. Oral alpha-tocopherol supplementation inhibits lipid oxidation in established human atherosclerotic lesions. Free Radic Res 2003; 37: 1235–44.
16. Helmersson J, Arnlov J, Larsson A, Basu S. Low dietary intake of beta-carotene, alpha-tocopherol and ascorbic acid is associated with increased inflammatory and oxidative stress status in a Swedish cohort. Br J Nutr 2009; 101: 1775–82.
17. Pashkow FJ, Watumull DG, Campbell CL. Astaxanthin: a novel potential treatment for oxidative stress and inflammation in cardiovascular disease. Am J Cardiol 2008; 101: 58–68.
18. Nakano M, Onodera A, Saito E, Tanabe M, Yajima K, Takahashi J, et al. Effect of astaxanthin in combination with alpha-tocopherol or ascorbic acid against oxidative damage in diabetic ODS rats. J Nutr Sci Vitaminol 2008; 54: 329–34.
19. Iwamoto T, Hosoda K, Hirano R, Kurata H, Matsumoto A, Miki W, et al. Inhibition of low-density lipoprotein oxidation by astaxanthin. J Atheroscler Thromb 2000; 7: 216–22.
20. Fassett RG, Coombes JS. Astaxanthin in cardiovascular health and disease. Molecules 2012; 17: 2030–48.
21. Choi SK, Park YS, Choi DK, Chang HI. Effects of astaxanthin on the production of NO and the expression of COX-2 and iNOS in LPS-stimulated BV2 microglial cells. J Microbiol Biotechnol 2008; 18: 1990–6.
22. Khan SK, Malinski T, Mason RP, Kuhant R, Jacob RF, Fujioka K, et al. Novel astaxanthin prodrug CDX-085 attenuates thrombosis in mouse model. Thromb Res 2010; 126: 299–305.
23. Yoshida H, Yanai H, Ito K, Tomono Y, Koiked T, Tsukahara H, et al. Administration of natural astaxanthin increases serum HDL-cholesterol and adiponectin in subjects with mild hyperlipidemia. Atherosclerosis 2010; 209: 520–3.

24. Park JS, Chyun JH, Kim YK, Line LL, Chew BP. Astaxanthin decreased oxidative stress and inflammation and enhanced immune response in humans. Nutr Metab 2010; 7: 18.

25. Monroy-Ruiz J, Sevilla MA, Carrón R, Montero MJ. Astaxanthin-enriched diet reduces blood pressure and improves cardiovascular parameters in spontaneously hypertensive rats. Pharmacol Res 2011; 63: 44–50.

26. Preuss HG, Echard B, Yamashita E, Perricone NV. High dose astaxanthin lowers blood pressure and increases insulin sensitivity in rats: are these effects interdependent? Int J Med Sci 2011; 8: 126–38.

27. Hussein G, Nakamura M, Zhao Q, Iguchi T. Anti-hypertensive effects and neuro-protective effects of astaxanthin in experimental animals. Biopharm Bull 2005; 28: 47–52.

28. Chew EY, Clemons TE, Agrón E, Sperduto RD, Sangiovanni JP, Davis MD, et al. Ten-year follow-up of age-related macular degeneration in the age-related eye disease study: AREDS report no.36. JAMA Ophthalmol 2014; 132: 272–7.

29. The Alpha-Tocopherol Beta Carotene Cancer Prevention Study Group. The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. New Engl J Med 1994; 330: 1029–35.

30. Virtamo J, Pietinen P, Huttunen JK, Korhonen P, Huttunen JK, Virtanen MJ, et al. Incidence of cancer and mortality following alpha-tocopherol and beta-carotene supplementation: a post-intervention follow-up. JAMA 2003; 290: 476–85.

31. Omenn GS, Goodman G, Thornquist M, Grizzle J, Rosenberg L, Barnhart S, et al. The beta-carotene and retinol efficacy trial (CARET) for chemoprevention of lung cancer in high risk populations: smokers and asbestos-exposed workers. Cancer Res 1994; 54: 2038–43s.

32. Mercadante AZ, Egeland ES. Carotenoids with a C40 skeleton. In: Britton G, Liaaen-Jensen S, Pfander H, eds. In vitro of epoxy-xanthophylls in humans. Br J Nutr 2008; 100: 273–7.

33. Hashimoto T, Ozaki Y, Mizuno M, Yoshida M, Nishitani Y, Azuma T, et al. Pharmacokinetics of fucoxanthinol in human plasma after the oral administration of kombu extract. Br J Nutr 2012; 107: 1566–9.

34. Mordenti J. Man versus beast: pharmacokinetic scaling in mammals. J Pharm Sci 1986; 75: 1028–40.

35. Maeda H, Hosokawa M, Sashima T, Miyashita K. Dietary combination of fucoxanthin and fish oil attenuates the weight gain of white adipose tissue and decreases blood glucose in obese /diabetic KK-Ay mice. J Agric Food Chem 2007; 55: 7701–6.

36. Gammon MA, Gemello E, Riccioni G, D'Orazio N. Marine bioactives and potential applications in sport. Marine Drugs 2014; 12: 2357–82.

37. D'Orazio N, Gemello E, Gammon MA, DeGiroalamo M, Ficoneri C, Riccioni G. Fucoxanthin: a treasure from sea. Mar Drugs 2012; 10: 604–16.

38. Okada T, Mizonu Y, Sibayama S, Hosokawa M, Miyashita K. Antiobesity effects of Undaria lipid capsules prepared with phospholipids. J Food Sci 2011; 76: H2–6.

39. Abidov M, Ramazanov Z, Seifulla R, Grachev S. The effects of Xanthigen in the weight management of obese premenopausal women with non-alcoholic fatty liver disease and normal liver fat. Diabetes Obes Metab 2010; 12: 72–81.

40. Hashimoto T, Ozaki Y, Mizuno M, Yoshida M, Nishitani Y, Azuma T, et al. Pharmacokinetics of fucoxanthinol in human plasma after the oral administration of kombu extract. Br J Nutr 2012; 107: 1566–9.

41. Heilbronn LK, Noakes M, Clifton MP. Energy restriction and weight loss on very-low-fat diets reduce C-reactive protein concentrations in obese, healthy women. Atherosclerosis 2004; 10: 27–90.

42. Shoelson SE, Lee J, Goldfine AB. Inflammation and insulin resistance. J Clin Invest 2006; 116: 1793–801.

43. Matsuzawa Y, Shimomura I, Kihara S, Funahashi T. Importance of adipokines in obesity-related diseases. Horm Res 2003; 60: 56–9.

44. Nozaki M, Fukuhara A, Segawa K, Okuno Y, Abe M, Hosogai N, et al. NO dysregulates adipocytokine expression in 3T3-L1 adipocytes. Biochem Biophys Res Commun 2007; 364: 33–9.

45. Park HJ, Lee MK, Park YB, Shin YC, Choi MS. Beneficial effects of Undaria pinnatifida ethanol extract on diet-induced-insulin resistance in C57BL/6J mice. Food Chem Toxicol 2010; 13: 557–63.

46. Ikeda K, Kitamura A, Machida H, Watanabe M, Negishi H, Hiraoka J, et al. Effect of Undaria pinnatifida on the development of cerebrovascular diseases in stroke prone spontaneously hypertensive rats. Clin Exp Pharmacol Physiol 2003; 30: 44–8.

47. Riccioni G, D’orazio N, Speranza L, Franceschelli S. Marine carotenoids and CV risk markers. Mar Drugs 2011; 9: 1166–75.

48. Tsukui T, Konno K, Hosokawa M, Maeda H, Sashima T, Mishayashi K, Fucoxanthin and fucoxanthinol enhance the amount of docosa-hexaenoic acid in liver of KK/Ay ob/ob diabetic mice. J Agric Food Chem 2007; 55: 5025–9.

49. Hadley CW, Clinton SK, Schwartz SJ. The consumption of processed tomato products enhances plasma lycopene concentrations in association with a reduced lipoprotein sensitivity to oxidative damage. J Nutr 2003; 133: 727–32.

50. Rissanen TH, Voutilainen S, Nyyssonen K, Salonen R, Kaplan GA, Salonen JT. Serum lycopene concentrations and carotid atherosclerosis: the Kuopio ischaemic heart disease risk factor study. Am J Clin Nutr 2003; 7: 133–8.
59. Adams CK, Campbell JK, Zaripheh S, Jeffery EH, Erdman JW. The tomato as a functional food. J Nutr 2005; 135: 1226–30.

60. Omoni AO, Aluko RE. The anti-carcinogenic and anti-atherogenic effects of lycopene. Trends Food Sci Tech 2005; 16: 344–50.

61. Rissanen TH, Voutilainen S, Nyssonen K, Salonen R, Salonen JT. Low plasma lycopene concentration is associated with increased intima-media thickness of the carotid artery wall. Arterioscler Thromb Vasc Biol 2000; 20: 2677–81.

62. Grobusch KK, Laufer LJ, Geleijnse JM, Boeing H, Hofman A, Witteman JC. Serum carotenoids and ATS: the Rotterdam study. Atherosclerosis 2000; 148: 49–56.

63. Rissanen TH, Voutilainen S, Nyssonen K, Salonen JT. Lycopene, atherosclerosis, and coronary heart disease. Exp Biol Med 2002; 227: 900–7.

64. Sesso HD, Liu S, Gaziano JM, Buring JE. Dietary lycopene, tomato-based food products and cardiovascular disease in women. J Nutr 2003; 133: 2336–41.

65. Kaliara AC, Dedousis GV, Schmidt H. Dietary antioxidants in preventing atherogenesis. Atherosclerosis 2006; 187: 1–17.

66. Stahl W, Sies H. Lycopene: a biologically important carotenoid for humans? Arch Biochem Biophys 1996; 336: 1–9.

67. Riccioni G, Bucciarelli T, D’Orazio N, Palumbo N, DiIlio E, Corradi F, et al. Plasma Antioxidants and asymptomatic carotid atherosclerotic disease. Ann Nutr Metab 2008; 53: 86–90.

68. Agarwal S, Rao AV. Tomato lycopene and low density lipoprotein oxidation: a human dietary intervention study. Lipids 1998; 33: 981–4.

69. Martin KR, Wu D, Meydani M. The effect of carotenoids on the expression of cell surface adhesion molecules and binding of monococytes to human aortic endothelial cells. Atherosclerosis 2000; 150: 265–74.

70. Loppnow H, Westphal E, Buchorn R, Wessel A, Werdan K. The effect of carotenoids on the expression of cell surface adhesion molecules and inflammatory cytokines in vivo. J Nutr 2001; 131: 2–9.

71. Chi H, Messas E, Levine RA, Graves DT, Amar S. IL-1 receptor signaling mediates atherosclerosis associated with bacterial exposure and/or a high-fat diet in a murine apolipoprotein E heterozygote model: pharmacotherapeutic implications. Circulation 2004; 110: 1678–85.

72. Libby P. Inflammation in ATS. Nature 2002; 420: 868–74.

73. Hu MY, Li YL, Jiang CH, Liu ZQ, Qu SL, Huang YM. Lycopene, atherosclerosis, and coronary heart disease. Exp Biology 2002; 227: 900–7.

74. Libby P. Inflammation in ATS. Nature 2002; 420: 868–74.

75. Renzoni E, Koeth R, Levison DA, Martens WS, Richelsen B, Bailey AL, et al. Lycopene metabolism in humans: a comprehensive study on the absorption, distribution, and excretion of lycopene in humans. J Lipid Res 2007; 48: 2372–86.

76. Renzoni E, Koeth R, Levison DA, Martens WS, Richelsen B, Bailey AL, et al. Lycopene metabolism in humans: a comprehensive study on the absorption, distribution, and excretion of lycopene in humans. J Lipid Res 2007; 48: 2372–86.

77. Gartner C, Stahl W, Sies H. Lycopene is more bioavailable from tomato paste than from fresh tomato. Am J Clin Nutr 1997; 66: 116–22.

78. Graziani G, Pernice R, Lanzuise S, Vitaglione P, Anese M, Fogliano V. Effect of peeling and heating on carotenoid content and antioxidant activity of tomato and tomato-virgin olive oil systems. Eur Food Res Technol 2003; 216: 116–21.

79. Christen WG, Liu S, Glynn RJ, Longe FJ. Lutein and docosahexaenoic acid prevent cortex lipid peroxidation in streptozotocin-induced diabetic rat cerebral cortex. Neuroscience 2010; 166: 271–8.

80. Chiu CT, Taylor A. Nutritional antioxidants, dietary carbohydrates, age-related maculopathy and cataract. Preventive nutrition: comprehensive guide for health professionals. Hum Press 2010; 4: 501–44.

81. Christen WG, Liu S, Glynn RJ, Longe FJ. Lutein and docosahexaenoic acid prevent cortex lipid peroxidation in streptozotocin-induced diabetic rat cerebral cortex. Neuroscience 2010; 166: 271–8.

82. Chiu CT, Taylor A. Nutritional antioxidants, dietary carbohydrates, age-related maculopathy and cataract. Preventive nutrition: comprehensive guide for health professionals. Hum Press 2010; 4: 501–44.

83. Christen WG, Liu S, Glynn RJ, Longe FJ. Lutein and docosahexaenoic acid prevent cortex lipid peroxidation in streptozotocin-induced diabetic rat cerebral cortex. Neuroscience 2010; 166: 271–8.

84. Chiu CT, Taylor A. Nutritional antioxidants, dietary carbohydrates, age-related maculopathy and cataract. Preventive nutrition: comprehensive guide for health professionals. Hum Press 2010; 4: 501–44.

85. Christen WG, Liu S, Glynn RJ, Longe FJ. Lutein and docosahexaenoic acid prevent cortex lipid peroxidation in streptozotocin-induced diabetic rat cerebral cortex. Neuroscience 2010; 166: 271–8.

86. Christen WG, Liu S, Glynn RJ, Longe FJ. Lutein and docosahexaenoic acid prevent cortex lipid peroxidation in streptozotocin-induced diabetic rat cerebral cortex. Neuroscience 2010; 166: 271–8.

87. Christen WG, Liu S, Glynn RJ, Longe FJ. Lutein and docosahexaenoic acid prevent cortex lipid peroxidation in streptozotocin-induced diabetic rat cerebral cortex. Neuroscience 2010; 166: 271–8.

88. Christen WG, Liu S, Glynn RJ, Longe FJ. Lutein and docosahexaenoic acid prevent cortex lipid peroxidation in streptozotocin-induced diabetic rat cerebral cortex. Neuroscience 2010; 166: 271–8.

89. Christen WG, Liu S, Glynn RJ, Longe FJ. Lutein and docosahexaenoic acid prevent cortex lipid peroxidation in streptozotocin-induced diabetic rat cerebral cortex. Neuroscience 2010; 166: 271–8.

90. Christen WG, Liu S, Glynn RJ, Longe FJ. Lutein and docosahexaenoic acid prevent cortex lipid peroxidation in streptozotocin-induced diabetic rat cerebral cortex. Neuroscience 2010; 166: 271–8.

91. Christen WG, Liu S, Glynn RJ, Longe FJ. Lutein and docosahexaenoic acid prevent cortex lipid peroxidation in streptozotocin-induced diabetic rat cerebral cortex. Neuroscience 2010; 166: 271–8.

92. Christen WG, Liu S, Glynn RJ, Longe FJ. Lutein and docosahexaenoic acid prevent cortex lipid peroxidation in streptozotocin-induced diabetic rat cerebral cortex. Neuroscience 2010; 166: 271–8.

93. Christen WG, Liu S, Glynn RJ, Longe FJ. Lutein and docosahexaenoic acid prevent cortex lipid peroxidation in streptozotocin-induced diabetic rat cerebral cortex. Neuroscience 2010; 166: 271–8.

94. Christen WG, Liu S, Glynn RJ, Longe FJ. Lutein and docosahexaenoic acid prevent cortex lipid peroxidation in streptozotocin-induced diabetic rat cerebral cortex. Neuroscience 2010; 166: 271–8.

95. Christen WG, Liu S, Glynn RJ, Longe FJ. Lutein and docosahexaenoic acid prevent cortex lipid peroxidation in streptozotocin-induced diabetic rat cerebral cortex. Neuroscience 2010; 166: 271–8.

96. Christen WG, Liu S, Glynn RJ, Longe FJ. Lutein and docosahexaenoic acid prevent cortex lipid peroxidation in streptozotocin-induced diabetic rat cerebral cortex. Neuroscience 2010; 166: 271–8.
96. Kritchevsky SB, Tell GS, Shimakawa T. Provitamin A carotenoid intake and carotid artery plaques: the atherosclerosis risk in communities study. Am J Clin Nutr 1998; 68: 726–33.
97. McQuillan BM, Hung J, Beilby JP. Antioxidant vitamins and the risk of carotid atherosclerosis. The perth carotid ultrasound disease assessment study (CUDAS). J Am Coll Cardiol 2001; 38: 1788–94.
98. Dwyer JH, Navab M, Dwyer KM. Oxygenated carotenoid lutein and progression of early ATS: the Los Angeles atherosclerosis study. Circulation 2001; 103: 2922–42.
99. Dwyer JH, Paul-Labrador MJ, Fan J. Progression of carotid intima-media thickness and plasma antioxidants: the Los Angeles atherosclerosis study. Arterioscler Thromb Vase Biol 2004; 24: 313–19.
100. Hozawa A, Jacobs JDR, Steffes MW, Gross MD, Steffen LM, Lee DH. Circulating carotenoid concentrations and incident hypertension: the coronary artery risk development in young adults (CARDIA) study. J Hypertens 2009; 27: 237–42.
101. Moens AL, Claeyjs MJ, Timmermans JP, Vrints CJ. Myocar-
102. Saeed SA, Waqar MA, Zubairi AJ, Bhurgri H, Khan A,
103. Adluri RS, Thirunavukkarasu M, Zhan L, Maulik N,
104. Voutilainen S, Nurmi T, Mursu J, Rissanen TH. Carotenoids
105. Zweier JL, Talukder MA. The role of oxidants and free radicals in reperfusion injury. Cardiovasc Res 2006; 70: 181–90.
106. Voutilainen S, Nurmi T, Mursu J, Rissanen TH. Carotenoids and cardiovascular health. Am J Clin Nutr 2005; 82: 451–60.
107. Johnson EJ. The role of carotenoids in human health. Nutr Clin Care 2002; 5: 56–65.
108. Giblin FJ. Glutathione: a vital lens antioxidant. J Ocul Physiol Opt 1999; 19: 192–201.
109. Tanumihardjo SA, Yang Z. Carotenoids: epidemiology of health effects. In: Caballero B, Allen L, eds. Encyclopedia of human nutrition. 2nd ed. Oxford: Elsevier Ltd; 2005, pp. 339–345.
110. Johnson EJ. The role of carotenoids in human health. Nutr Clin Care 2002; 5: 56–65.
111. Pattison DJ, Symmons DPM, Lunt M, Welch A, Bingham SA, Day NE, et al. Dietary b-carotene and inflammatory polyarthritides: results from a population-based prospective study. Am J Clin Nutr 2005; 82: 451–5.
112. Cerhan JR, Saag KG, Merlino LA, Mikuls TR, Criswell L. Antioxidant micronutrients and risk of rheumatoid arthritis in a cohort of older women. Am J Epidemiol 2003; 157: 345–54.
113. Kritchevsky SB, Bush AJ, Pahor M, Gross MD. Serum carotenoids and markers of inflammation in non-smokers. Am J Epidemiol 2000; 152: 1065–71.
114. Suzuki K, Ito Y, Ochiai J. Relationship between obesity and serum markers of oxidative stress and inflammation in Japanese. Asian Pac J Cancer Prev 2003; 4: 259–66.
115. Ross AC, Zolfaghari R, Weisz J. Vitamin A: recent advances in the biotransformation, transport, and metabolism of retinoids. Curr Opin Gastroenterol 2001; 17: 184–92.
116. Jialal I, Norkus EP, Cristol L, Grundy SM. Beta-Carotene inhibits the oxidative modification of low-density lipoprotein. Biochem Biophys Acta 1991; 1086: 134–8.
117. Robbins M, Topol EJ. Inflammation in acute coronary syndromes. Cleve Clin J Med 2002; 69: 130–42.
118. DiTomo P, Canali R, Ciavardelli D, DiSilvestre S, DeMarco A, Giardinelli A, et al. B-carotene and lycopene affect endothelial response to TNF-a reducing nitro-oxidative stress and interaction with monocytes. Mol Nutr Food Res 2011; 55: 1–11.
119. Aizawa T, Wei H, Miano JM, Abe J. Role of PDE-3 in NO/cGMP-mediated anti-inflammatory effects in vascular smooth muscle cells. Circ Res 2003; 93: 406–13.
120. Shaish A, Harari A, Hananshivi L, Cohen H, Bitzur R, Luvish T, et al. 9-cis beta-Carotene-rich powder of the alga Dunaliella bardawil increases plasma HDL-c in fibrate treated patients. Atherosclerosis 2006; 189: 215–21.
121. Harari A, Harats D, Marko D, Cohen H, Barshack I, Kamari Y, et al. A 9-cis b-Carotene–enriched diet inhibits atherogenesis and fatty liver formation in LDL-R knockout mice. J Nutr Dis 2008; 138: 1923–30.
122. Hubacek JA, Bobkova D. Role of cholesterol 7alpha-hydroxylase (CYP7A1) in nutrigenetics and pharmacogenetics of cholesterol lowering. Mol Diagn Ther 2006; 10: 93–100.
123. Racchioni G, D’Orazio N, Palusmo N, Bucciarelli V, Dilio E, Bazzano LA, et al. Relationship between plasma antioxidant concentrations and carotid intima-media thickness: the asymptomatic carotid atherosclerotic disease in Manfredonia study. Eur J Card Prev Rehabil 2009; 16: 351–7.
124. Lobo GP, Amengual J, Li HNM, Golczak M, Bonet ML, Palczewski K, et al. Beta-Carotene decreases PPR–alpha activity and reduces lipid storage capacity of adipocytes in a beta-carotene oxygenase 1-dependent manner. J Biol Chem 2010; 285: 27891–99.
125. Schwarz EJ, Reginato MJ, Shao D, Krakow SL, Lazar MA. Retinoic acid blocks adipogenesis by inhibiting C/EBPbeta-mediated transcription. Mol Cell Biol 1997; 17: 1552–61.
126. Mercader J, Granados N, Bonet ML, Palou A. All-trans retinoic acid decreases murine adipose retinol binding protein 4 production. Cell Physiol Biochem 2010; 22: 363–72.
127. Ramakrishna V, Jailkhani R. Oxidative stress in non insulin dependent diabetes mellitus (NIDDM) patients. Acta Diabetol 2008; 45: 41–6.
128. Musch DC. Evidence for including lutein and zeaxanthin in diet for patients with age related macular degeneration. JAMA Ophthalmol 2014; 132: 139–41.