

## Prevention of cardiovascular diseases with carotenoids

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### 1. ABSTRACT

Oxidative stress is a key contributor to the development of cardiovascular diseases. Bioactive dietary elements including phytochemicals, and in particular, carotenoids display antioxidant effect and substantially reduce markers of oxidative stress. Carotenoids have been shown to prevent several chronic disorders including cardiovascular diseases by reducing the inflammatory responses. Here, we discuss the use of traditional and novel carotenoids in prevention of cardiovascular disease.

### 2. INTRODUCTION

A compromised endogenous antioxidant defense mechanism can lead to an imbalance between production and removal of radical oxygen species (ROS). An excessive oxidative stress and persistent low-level inflammation in the cardiovascular system, thus resulting in chronic phlogosis, cell damage and death, contribute to the development of cardiovascular diseases (CVD), such as hypertension, atherosclerosis, micro-angiopathy and cardiovascular accidents (1) such as coronary artery disease, stroke and myocardial infarction (2). In fact, CVD result from a *continuum* of pathophysiological events, advancing from local redox disequilibrium to endothelial dysfunction, vassal inflammation and excessive vascular remodeling with subsequent cellular damage (3).

In this respect, not only pharmacology but also physical exercise and dietary interventions can play a crucial role in cardiovascular prevention through increasing cellular anti-oxidant system expression and targeting oxidative stress and chronic

inflammation (4). In particular, a nutritional preventive strategy through antioxidants represents a new frontier both in prevention and treatment of atherosclerosis and, consequently of CVD. In fact, the production of oxidized low-density cholesterol (LDL) can be countered by dietary carotenoids, which are acceptor molecules sequestering free radical electrons, thus preventing LDL oxidation (5).

Scientific evidences display a strong link between oxidative stress, with a related pro-inflammatory systemic environment, and CVD (6). In this respect, an augmented consumption of antioxidant-rich fruits and vegetables can be protective against cardiovascular disease. Life-style plays a crucial role in preventing chronic inflammatory disorders (7), especially CVD (8). For example, thrombotic pathology is consequent to traditional and well-known risk factors: genetic factors, age, but also smoking, hypertension, dyslipidemia, insulin resistance, diabetes, overweight and obesity (9). However, novel risk factors have been recently identified, such as high sensitivity C-reactive protein and other markers of inflammation, such as homocysteine, and lipoprotein-a (10). Consequently, a dietetic intervention should be the initial approach against CVD. In this respect, carotenoids may play an important role in cardiovascular prevention and in health maintenance (11, 12): as part of a balanced diet, these nutrients are responsible, directly but also indirectly, through a synergistic cooperation with other antioxidants (13), for the Mediterranean diet's advantages and health benefits (14). This provides further motivation for nutritional improvements that can increase longevity and even enhance human life quality.

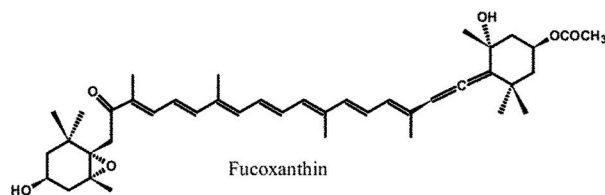


Figure 1. The molecular structure of the terrestrial carotenoid lycopene.

### 3. ANTIOXIDANT ACTIVITY OF CAROTENOIDS

Carotenoids are a class of natural fat-soluble pigments, largely widespread in the vegetable kingdom and present in high concentrations in algae and microorganisms. The wider family of carotenoids includes more than 500 members, of which 50 are present in our food, but only 20 are absorbed in the intestine and can reach our bodily tissues (6). They are classified, according to their chemical structure, into carotenes and xanthophylls.

Carotenes include  $\beta$ -carotene and lycopene and xanthophylls include lutein, fucoxanthin, canthaxanthin, zeaxanthin,  $\beta$ -criptoxanthin, capsorubin, and astaxanthin (15). However, the carotenoid species so far analyzed amount to an exiguous number. Not only terrestrial but also marine carotenoids, showed various healthy beneficial effects on humans. In this respect, novel marine carotenoids are gaining attention as potential development materials for functional foods, in order to prevent cardiovascular diseases.

Carotenoids are stored in several human tissues: cervix, lung, skin, eye but especially liver and adipose tissue. In particular, tissues containing more low-density lipoprotein receptors (LDL-R) accumulate great quantities of carotenoids, maybe because of a non-specific uptake by lipoprotein carriers (10). Carotenoids have potential antioxidant biological properties due to their chemical structure and interaction with biological membranes. Numerous epidemiologic studies asserted that antioxidants could be used as an inexpensive means of prevention of cardiovascular diseases, although interventional trials' results gave not only positive findings, but also null results, and even some hypothesis of harm in certain high-risk populations. The antioxidant activities of carotenoids are considered the main mechanism of their beneficial health effects (16), however, carotenoids are involved in a complex metabolism thus responding to systemic forces. For instance, carotenoids' plasmatic levels result to be lower in both active and passive cigarette smokers because of their free radicals-rich microenvironment, and higher in people following a "Mediterranean" dietetic pattern because of their major fruits and vegetables intake.

Carotenoids are excellent light filters and efficient quenchers of both singlet oxygen and excited triplet state molecules. Their lipophilicity and their subsequent characteristic sub-cellular distribution makes them efficient photo-protectants: they absorb light, thus providing photo-protection and contrasting photo-oxidative damage to photo-synthetic organisms, eye (macula protection is mostly performed by the xanthophylls zeaxanthin and lutein) and skin (whose protection mostly involves the carotenes  $\beta$ -carotene and lycopene). Their antioxidant activity is due to their ability to quench singlet oxygen, to be oxidized, and to be isomerized (17). They scavenge reactive free radicals and become carotenyl radicals after reaction through a hydrogen abstraction: this process can lead to a switch from a beneficial antioxidant process to a damaging pro-oxidative one (18). This antioxidant role has been suggested to be one of the mechanisms for carotenoids' preventive effects against CVD but they exert also other beneficial effects.

### 4. CAROTENOIDS AND BENEFICIAL CARDIOVASCULAR EFFECTS

Oxidative stress and a persistent chronic low level inflammation in the cardiovascular system, certainly contribute to the development of cardiovascular diseases.

Oxidatively modified low-density lipoproteins (LDL) are involved in the initiation and promotion of atherosclerosis and coronary heart disease. Atherogenesis seems to be due to foam cell production by the introduction of a source of free radicals that cause LDL oxidation. Thus, protection from LDL oxidation by antioxidants may lead to protection against human coronary heart disease. Considering that  $\beta$ -carotene and lycopene are primarily transported in LDL, it has they are in the central position to protect LDL from oxidation (19). The strongest population-based evidence comes from the study EURAMIC that evaluated the relationship between adipose tissue antioxidant status and acute myocardial infarction in more than 1500 subjects from 10 different European countries. Its results displayed a dose-response relationship between adipose tissue lycopene and the risk of myocardial infarction. In this multicenter-case-control study of antioxidants role, lycopene (Figure 1) was displayed to clearly contribute to the cardioprotective effect, much more than  $\beta$ -carotene. The protective potential of lycopene was maximum among individuals with highest polyunsaturated fat stores (20). In fact, lycopene results to be inversely associated to the calcified plaques of the abdominal aorta and directly related to a reduced carotid intima-media thickness and lower incidences of myocardial infarction and stroke (21).

Another study comparing the Lithuanian and Swedish populations demonstrated lower lycopene levels

to be associated with increased cardiovascular risk and mortality from coronary heart disease (22). Lycopene was also shown to significantly reduce the levels of oxidized LDL in subjects consuming tomato sauce and juice as sources of lycopene. In another small study, lycopene was shown to reduce serum total cholesterol levels, thus decrementing CVD (22).

The anti-atherogenic effect of lycopene is associated with anti-inflammatory activities, improved lipid homeostasis, minor adhesion molecules expression and interactions between monocytes and endothelial cells (23) by inhibiting IL-1 secretion, which is a key factor in inflammatory processes inducing the synthesis of other pro-inflammatory cytokines and acute-phase proteins with the following recruitment of leukocytes to the intima in the early atherosclerotic lesions (24). In addition, lycopene positively influences nitric oxide levels, contributing to vasodilatation, even resulting in a more effective slowing of the progression of atherosclerosis than by fluvastatin (25).

The Beijing atherosclerosis study and the Los Angeles Atherosclerosis study displayed an inverse association between lutein and initial atherosclerosis; further studies showed that higher levels of plasma zeaxanthin (inversely correlated with right common carotid artery stiffness, pulse wave velocity and elastic modulus) may be protective against early atherosclerosis (26). Lutein's benefits on heart and blood vessels consists also in preventing hypertension: higher lutein plasmatic levels are associated to lower baseline systolic blood pressure, independently of smoking status (27). In addition, lutein brings therapeutic benefits in case of cardiovascular complications. In fact, it limits myocardial ischemia/reperfusion injury by decreasing oxidative stress and myocytes apoptosis (28), thus preventing contractile dysfunction and reducing cardiovascular morbidity.

Similarly, higher plasmatic levels of  $\beta$ -carotene are associated with increased cGMP levels and NO bioavailability, which lead to a down-regulation of NF- $\kappa$ B-dependent adhesion molecules in endothelial cells (29). The 9-cis-  $\beta$ -carotene in a combined treatment of dyslipidemia enhanced the effect of the drug bezafibrate on HDL elevation in human apolipoprotein (30). This isomer significantly reduced mRNA levels of CYP7a, the rate-limiting enzyme of bile acid synthesis (31) consequently reducing cholesterol absorption in intestine; it also decreased 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.

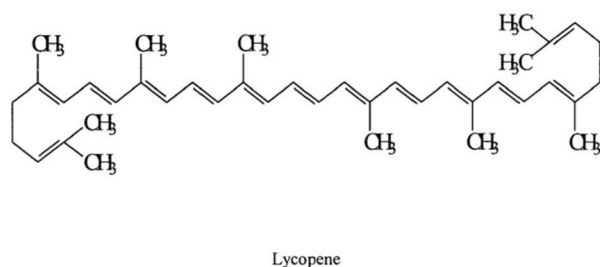
Very recently, the longitudinal association of regular intake of vitamin E, C, D, B9, carotenoids and minerals with levels of HbA1c has been investigated

in the general non-diabetic population. The results indicate that there is an inverse association of regular carotenoid intakes above 6.8. mg/d with concentrations of HbA1c after 10 years and no significant association with the other investigated vitamins and minerals (32). The observed reduction of 0.3. % in HbA1c levels can be considered clinically relevant, considering that a reduction of 0.1.% in the general non-diabetic population could lead to a reduction in mortality of up to 6% over a period of 6 years (33).

Similar dose–effect results were emerged from the Epidemiology of Vascular Ageing (EVA) study, which investigated plasma carotenoid levels with regard to other diabetes/cardiovascular-related outcomes in elderly volunteers (34): the risk of dysglycemia was significantly lower in presence of highest plasma carotenoids' levels after 9 years of follow-up. A potential mechanism for this HbA1c-lowering effect of carotenoids might be their antioxidant activity, which is closely related to protein glycosylation. Larger prospective studies on carotenoids intake and blood levels and HbA1c concentrations are needed to confirm these results. If a significant inverse association of higher carotenoid intakes with HbA1c levels will be confirmed, carotenoids might represent a useful strategy in preventing the development of type 2 diabetes as well as cardiovascular complications and mortality in the general population.

Recently there was a dramatic increase in the global-market demand for carotenoids, thus determining a significant rise in algae exploration. Well-known marine entities, such as astaxanthin,  $\beta$ -cryptoxanthin, zeaxanthin and fucoxanthin are recognized antioxidant, undoubtedly helpful in cardiovascular prevention. In particular, astaxanthin improves blood lipid profile by increasing high-density lipoprotein cholesterol, decreasing LDL-cholesterol, triglycerides, as well as lipid peroxidation (35) and inflammation markers (after 8 weeks, subjects taking 2 mg/day had lower hs-CRP which is considered an important indicator of heart disease) (36) in correlation with increased adiponectin in humans. Another cardiovascular benefit is a significant blood pressure lowering for its modulatory effects on nitric oxide (37): oral administration of astaxanthin for 5 weeks showed to delay the incidence of stroke in spontaneously hypertensive rats (38). Also a diet rich in fucoxanthin could be protective through the augmentation of thermogenesis, with subsequent overweight inhibition (11), through the regulation of cytokine secretions from white adipose tissue and through the promotion of docosahexaenoic acid synthesis (39) resulting in improvements in lipid profile and a healthy liver function (40). In fact, long-term unbalanced diets alter lipid metabolism and leads to the accumulation of visceral fat, thus resulting in obesity-related metabolic diseases, such as hypertension, dyslipidemia and cardiovascular pathologies.

## Carotenoids, the prevention from the sea



**Figure 2.** The molecular structure of the marine carotenoid fucoxanthin.

In this respect, fucoxanthin (Figure 2) can play a crucial role through several mechanisms (11). Fucoxanthin significantly reduces plasmatic triglyceride concentrations and positively influences cholesterol-regulating enzymes such as 3-hydroxy-3-methylglutaryl-coenzyme A reductase and acyl-coenzyme A (41). Fucoxanthin also affects lipid metabolism gene expression: its supplementation in murine models decreased mRNA expression of hepatic acetyl-CoA carboxylase (ACC), a biotin-dependent enzyme that up-regulates the metabolism of fatty acids.

Fucoxanthin increased High-Density Lipoprotein (HDL)-cholesterol levels in KK-Ay mice (a type 2 diabetic knock-out mouse model that exhibits glucose intolerance, severe insulin resistance, dyslipidemia, hypertension and, consequently, a marked cardiovascular risk) by inducing Sterol Regulatory Element-Binding Protein (SREBP) expression and reduced cholesterol uptake in the liver, via down-regulation of Low-Density Lipoprotein (LDL)-receptor and Scavenger Receptor class B member 1 (SR-B1). In addition, dietary fucoxanthin significantly augmented the mRNA expression of protein convertase subtilisin/kexin type 9 (PCSK9), which enhances intralysosomal degradation of LDL-R (42). Fucoxanthin supplementation also decreased mRNA expression of fatty acid synthase (FAS), a multi-enzyme protein that catalyzes fatty acid synthesis, which has been investigated as a chemotherapeutic target, but it may also be implicated in the production of an endogenous ligand of the nuclear receptor PPAR- $\alpha$ , the target of the fibrate drugs against hyperlipidemia (43), which is an important cardiovascular risk marker too.

In addition, new and rare sea-derived resources are emerging. Among these, siphonaxanthin is a specific keto-carotenoid, found in edible green algae such as *Codium fragile*, *Caulerpa lentillifera*, and *Umbraulva japonica*. In studies on human umbilical vein endothelial cells and the rat aortic ring, siphonaxanthin displayed a significant anti-angiogenic activity, due to a mRNA expression down-regulation of fibroblast growth factor 2 (FGF-2), its receptor FGFR-1, and their trans-activation factor (44). If we consider atherosclerotic plaque

progression and vulnerability to rupture, angiogenesis represents a source of intraplaque hemorrhage.

This potential prevention of angiogenesis and remodeling under pathological conditions, such as cancer and atherosclerosis (45), results in a promising prevention approach against inflammatory diseases.

Very recently, two rare carotenoids, saproxanthin and myxol have been extracted respectively from *Saprospira grandis* and cyanobacterium *Anabaena variabilis* (46) and reported to possess powerful antioxidant properties. Their strong antioxidant potential, even superior to those of zeaxanthin and  $\beta$ -carotene (47), is explained by their inhibitory activity on lipid peroxidation induced by free radicals in rat brain (48).

Therefore, saproxanthin and myxol can determine reinforcement and stabilization of biological membranes, which decreases their permeability to oxygen and enhances protection against radical-induced peroxidation. These novel rare monocyclic marine carotenoids, with a  $\gamma$ -carotene skeleton in their structure, need to be further evaluated for their potential as development materials for both pharmaceuticals and functional foods, in order to prevent oxidative stress-related disorders such as and cardiovascular diseases.

## 5. CONCLUSIONS

CVD pathophysiology is dominated by inflammation and oxidative stress. Apart from invariable factors such as sex, age, and genetics, life-style and dietary intervention represent crucial preventing strategies against cardiovascular risk factors. It would be necessary not only to practice regular physical exercise, reduce sodium and cholesterol dietary intake, and avoiding smoking, but also a wider antioxidants intake (49), especially vitamin C and E, polyphenols and carotenoids. In fact, inflammatory pathologies derive from a continuum of patho-physiological processes: cardiovascular diseases advance from a local redox disequilibrium to endothelial dysfunction, inflammation, and excessive vascular remodeling, which slowly leads to atherosclerosis and subsequent cardiovascular accidents such as coronaropathy, myocardial infarction and ischemic/hemorrhagic stroke. A nutritional approach through natural antioxidant substances represents an important new frontier in both the prevention and treatment of cardiovascular diseases. Carotenoids are quenchers of free radicals, ROS and NOS, thus their antioxidant and anti-inflammatory activity may help against cardiovascular risk factors such as markers of inflammation, hyperlipidemia, hypertension, insulin resistance and obesity. Consequent reduction of blood pressure baseline levels and inflammation, as well as correction in lipid profile can lead to cardiovascular health's benefits. This potential preventive and therapeutic

strategy can certainly reduce the risk of developing CVD, with promising applications and without side effects.

In conclusion, the beneficial effects of carotenoids have been widely reported, not only in cardiovascular prevention, but also in alcoholic liver injury, cancer (50) and 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.

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