Carotenoids[1]

Approximately 600 unique carotenoids can be found in plant species, as well as select species of algae and fungi. In plants and animals, carotenoids serve as pigments, responsible for the varied and vivid colors present in nature. Because their presence is so obvious, carotenoids were some of the earliest studied phytochemicals (1). Health scientists have identified a wide range of functions, from optical enhancement within the eye to immunomodulatory and antioxidant functions. Each of these functions can manifest differently across the life span. For example, carotenoids may influence prenatal development and maturation [for review, see Hammond (2)] as well as disease risk in older adults (3). Carotenoids may also have the capability to be used as selective vehicles for drug delivery to target tissues, such as lutein, which has been used to deliver pharmaceutical agents to the neural retina (4).

Plants can be selectively bred to contain higher carotenoid content, making them better sources of the carotenoid in question, and can be supplemented in the human diet to influence development, maturation, and nutritional status. One example is β-carotene. β-Carotene is a member of the carotene family, which has no polar functional groups and can be cleaved in liver into 2 vitamin A molecules. Vitamin A can be toxic in high doses. β-Carotene, however, can be supplemented in many individuals with reduced concern of toxicity. Vitamin A deficiency is still common in developing countries like many in Southeast Asia, where some 250,000 children a year have night blindness due to vitamin A deficiency and about half that number dies in any given year. White rice can be genetically modified to contain a higher content of β-carotene in the endosperm of the grain, which gives it a yellow color responsible for the name "golden rice." Modifying white rice to have higher carotenoid content may be a means of inexpensively reducing vitamin A deficiencies in many developing countries where rice is a staple (5).

Carotenoids were first chemically characterized by Willstatter in 1907 (1). He correctly classified the 2 major groups, the carotenes, which are hydrocarbons such as β-carotene and lycopene ($C_{40}H_{56}$), and the xanthophylls, which include oxygen in addition to hydrogen and carbon ($C_{40}H_{56}O_2$). Xanthophylls, which are essentially oxidation products of the carotenes, include lutein, zeaxanthin, canthaxanthin, and β-cryptoxanthan. Carotenoids have a conjugated polyene structure that allows electrons in the double bonds to easily delocalize, lowering the ground state of the molecule. This core system of conjugated carbon-carbon bonds makes carotenoids efficient quenchers of singlet oxygen. This structure also creates a lipophilicity that causes the pigments both to retard lipid peroxidation and stabilize lipid-protein structures like cell membranes.

Mammals cannot synthesize carotenoids de novo, and, therefore, carotenoids must be obtained from diet. Dietary intake of carotenoids varies widely across individuals and cultures. For example, the average intake of β-carotene is ~1.9 mg/d for the Finnish but 17 mg/d for Fijian populations (6).

Deficiencies: There are ~34 carotenoids (this includes 13 geometric isomers and 8 metabolites) that are regularly identified in human serum and breast milk (7). In Americans, just 6 of these, β-carotene, lutein, β-crypotxanthin, lycopene, α-carotene and zeaxanthin, comprise ~90% of that total number (8). None of the carotenoids are considered essential nutrients. No carotenoid is directly involved in a vital metabolic pathway, nor has the relative absence of a carotenoid been linked exclusively to the induction of a specific deficiency or chronic disease (hence, the lack of FDA-approved "health claims").

Diet recommendations: Because carotenoids are not associated with deficiency states per se, they, like the vast majority of food components, have no formal recommendations for intake. It has been argued that some carotenoids (e.g., lutein and zeaxanthin) should be considered conditionally essential nutrients. In the case of lutein and zeaxanthin, ocular disease and retinal maturation have been considered outcomes (9), but this point remains debatable (10). The lack of formal recommendations, however, has led to a conspicuous incongruity: (a) an immense confluence of data linking carotenoid intake to health and the prevention of a number of acquired diseases; (b) populations with conditions that are strongly linked to a poor diet; and (c) a medical community that has no formal basis for making dietary recommendations (based on current evidentiary standards).

Food sources: Carotenoids are most concentrated in green leafy vegetables (e.g., kale, spinach, collards, and mustard greens) and colored fruits (e.g., kiwi, tomatoes). They tend to be most bioavailable when they are embedded in foods (or consumed simultaneously) that also have a lipid base (like the yolks of eggs) and when preparation (e.g., blending, heating) breaks down the cell walls of the plant (11).

Clinical uses: Carotenoids are rarely used as a specific therapy per se. Some exceptions are β-carotene used to reduce some of the deleterious effects of light in patients with erythropoietic protoporphyria (12) and lycopene used for infertility in men (13). It is more common that carotenoids are recommended as

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part of a healthy diet or as purified supplements to reduce the probability of acquired diseases like macular degeneration. It is also common for some carotenoids to be prescribed as palliatives. For example, lutein and zeaxanthin supplements are often recommended by ophthalmologists for the purpose of reducing the risk of eye disease and improving visual function (such as glare disability, discomfort, speeding photostress recovery).

Toxicity: Carotenoids are generally nontoxic, even when taken in high doses as purified supplements. There appear, however, to be a few exceptions. High doses of canthaxanthin can cause a reversible form of retinopathy (14). Also, high intake of β-carotene (in supplement form, 20–30 mg/d) is contraindicated for smokers due to the increased risk of lung and stomach cancer found in some studies (15). Excessive intake of some of the major carotenoids can also cause carotenemia, a reversible yellowing of the skin.

Recent research: There are literally hundreds of thousands of research studies that have investigated the role of carotenoids in human health, starting in the 1800s. Like many other phytochemicals, much of the research on carotenoids has been subject to experimental designs that are more appropriate to testing drug efficacy (16) and less appropriate to dietary compounds, to which the population is generally not "naive." Moreover, double-blind, placebo-controlled studies of phytochemicals are conducted over relatively short time periods, when it is more likely that relationships between phytochemicals and disease states are of a longer term nature. Carotenoids are ubiquitous components of food that tend to have small effects that aggregate over decades and work synergistically with many other components of a healthy lifestyle. Unlike many phytochemicals, however, carotenoids do have some characteristics that seem to be slightly more amenable to the immediacy required by today's "evidence-based" approach to medicine. For example, many chronic diseases are characterized by high levels of inflammation and oxidative stress (17). Carotenoids are some of the more potent lipid-based antioxidants in the diet and are also anti-inflammatories as measured against the inflammatory cytokine interleukin-6 as well as other markers of inflammation (18).

Carotenoids within the serum tend to associate with specific tissues in the body. For example, lycopene is concentrated in the prostate, β-carotene is concentrated in the corpus luteum, and lutein and zeaxanthin are concentrated in the neural retina and brain neocortex. There appears to be general consensus that, at those sites, carotenoids can retard disease development based on reducing oxidative/ inflammatory stress. Mortality studies show that high carotenoid intake significantly reduces all-cause mortality (3). Reduced mortality is likely linked to reduced risk of terminal diseases like cancer. Stress from reactive oxygen species has been shown to result in base modification (e.g., oxidized purine and pyrimidine), strand breakage, DNA protein cross-linkage, formation of micronuclei (19), all factors that promote cell dysplasia. If oxidative stress is an important factor in cancer initiation, carotenoids, as antioxidants, would certainly be prophylactic. Mignone et al. (20), for example, showed that individual carotenoids of various types were linked to a reduction in breast cancer risk of nearly 20%. Eliassen et al. (21) did a pooled analysis of 8 prospective studies and found a similarly sized effect for women with high levels of circulating carotenoids.

The biological actions of carotenoids may affect a given organism differently depending on developmental phase (2). For example, egg yolks are yellow because they accumulate carotenoids (largely lutein), which influence prenatal development by regulating the oxidative stress of the chick. Lutein supplementation in preterm infants (22) has been shown to significantly improve the α wave of retinal photic electroencephalography (the ability of rods to initiate a visual signal). On the other end of the age spectrum, degenerative disease often causes a cascade of oxidative/inflammatory stress. By reducing this stress to diseased tissue, the probability of deleterious progression might be reduced. For example, retinal lutein may help prevent the progression of geographic age-related macular degeneration to the more damaging neovascular form, by reducing oxidative stress (23).

Although many of the health effects of carotenoids seem to be linked to their antioxidant and inflammatory functions, carotenoids have a host of other functions that are significant (2). For example, because carotenoids absorb light, they can also influence the optical characteristics of the human eye. Lutein and zeaxanthin concentrate in the inner layers of the macular region of the eye (there, they are referred to as macular pigment). Macular pigment selectively absorbs the lower third of the visible spectrum (400–500 nm, peak absorbance = 460 nm). By forming an internal yellow filter that screens cones, a number of optical improvements occur. For example, by filtering scattered short-wave light, glare disability and discomfort are lessened (24). Light energy is inversely related to wavelength. Hence, by screening the energetic shorter wavelengths of light, actinic damage to the outer retina is reduced, whereas photostress recovery, chromatic contrast, and visual range are increased. The retina is part of the central nervous system, and lutein, in particular, also accumulates in brain. It obviously does not absorb light there, but it does appear to improve neural efficiency, resulting in faster visual processing and improved cognition (25).

Work on the immediate salubrious effects of carotenoids is bound to continue. Research on vulnerable populations such as preterm infants and efforts to understand effects on the brain (e.g., cognitive function) is also likely to accelerate. Due to a generally poor diet, there appears to be a growing paucity of carotenoids in tissues where, historically, levels were likely quite high. The ultimate effect on human biology is hard to define precisely, but there appears to be a general scientific consensus that it is negative.

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