Xanthophylls

Nutrient

Carotenoids are plant pigments commonly found in fruits and vegetables. They are made up of 2 classes, xanthophylls and carotenes. Whereas carotenes are composed of only carbon and hydrogen, xanthophylls include hydroxyl groups, making them slightly more hydrophilic than carotenes. Carotenoids are found throughout the body. Among the carotenoids, the xanthophylls lutein and zeaxanthin selectively accumulate in the eye and brain. In the eye, lutein and zeaxanthin are responsible for the yellow pigment of the macula lutea, along with the nondietary lutein metabolite *meso*-zeaxanthin (1). Xanthophylls have properties similar to lipids, being insoluble in water, and thus share similar transport mechanisms in the aqueous environment of the body. Many factors affect their bioavailability from the diet, including processing, meal composition and digestive enzyme activity (2). In the digestive tract, xanthophylls are incorporated into micelles and cross the enterocyte by simple passive diffusion or via several proposed lipid transporters. β-Cryptoxanthin, the only provitamin A xanthophyll, is partially cleaved to vitamin A by β-carotene-15,15′-oxygenase, while the other xanthophylls are incorporated into chylomicrons and secreted from the lymph into the blood. Xanthophylls are exclusively transported intact through the blood via lipoproteins and are taken up by tissues via membrane-bound lipid transporters. Very small amounts of the cleavage products of lutein and zeaxanthin are present in human plasma and are called "apocarotenoids" (1). Apocarotenoids are present in foods and there is evidence that they are bioactive in the body. Their presence in the body is either from the diet or by enzymatic activity of β, β-carotene-9′,10′-dioxygenase.

The presence and levels of xanthophyll in the blood and tissues are the result of dietary intake. Although considered nonessential nutrients, dietary intake is associated with decreased risks of cardiovascular disease, age-related macular degeneration (AMD), cognitive decline, and certain cancers (3–5). Because of the conjugated structure of carbon-carbon double bonds, xanthophylls quench reactive oxygen species, especially singlet oxygen, which can cause lipid peroxidation, DNA damage, and oxidative damage to important cellular pathways (1). Lutein and zeaxanthin assume a unique configuration in the macula of the eye, allowing their hydroxyl groups to form hydrogen bonds with polar head groups on ocular membranes. Here they effectively quench photoinduced singlet oxygen and attenuate damaging blue visible light. In the brain, lutein and zeaxanthin may combat free radical damage in an environment made vulnerable by a high PUFA content combined with high metabolic activity (6). The antioxidant properties of xanthophylls may minimize the damage from oxidative stress in these tissues, which may otherwise lead to inflammation and pathology.

Deficiencies

Inadequate intake of xanthophylls does not lead to deficiency-related health decline. However, studies in xanthophyll-free nonhuman primates report disturbances in the retinal pigment epithelial cells as well as increased retinal damage from blue light when compared with animals receiving lutein and zeaxanthin in their diet (3).

Dietary Recommendations

There are no specific dietary recommendations for xanthophylls. Based on the body of literature supporting ~6–10 mg/d of lutein and zeaxanthin, these xanthophylls may be important for eye health (1).

Food Sources

Dietary sources of xanthophylls include lutein and zeaxanthin in green leafy vegetables and corn, and β-cryptoxanthin in pumpkins, papayas, and peppers. The minor xanthophylls astaxanthin and canthaxanthin are found in certain fish and seashells, and in certain mushrooms (2). *Haematococcus pluvialis*, a green microalga, accumulates high amounts of astaxanthin and is used as a pigment source in farmed salmon, trout, and shrimp feed (7). Wild salmon is also a good source for astaxanthin.

Clinical Uses

Macular pigment (MP), composed of lutein and zeaxanthin, is believed to be important for visual function and may protect against AMD (1). MP may provide visual benefits beyond disease prevention, such as enhanced contrast sensitivity and improved glare disability (3). The Age-Related Eye Disease Study (AREDS) 2 supports the addition of 10 mg lutein and 2 mg zeaxanthin in a supplement to reduce the progression to advanced AMD. Thus, some ophthalmologists recommend lutein and zeaxanthin supplementation in AMD patients or in patients whose eye health may benefit.

Toxicity

Lutein, zeaxanthin, and astaxanthin are generally recognized as safe for use in the human diet as supplements or additives to other foods or feed for animals consumed by humans (1). No toxicity has been reported for β-cryptoxanthin. Choi et al. (8) published a case study in which bilateral "foveal sparkles" were reported in a woman who took a daily 20 mg lutein supplement for 8 y and had an unusually high dietary consumption of lutein. Seven months after discontinuing the lutein supplement, but continuing her dietary habits, the crystals resolved

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in one eye but not in the other. Retinopathy was reported as an adverse effect in those consuming >30 mg of canthaxanthin supplements, but this was reversed after discontinuation (9). Canthaxanthin is approved as a feed additive in the diets of certain animals, such as salmon and trout for flesh coloring and hens for egg yolk color.

Recent Research

Supplementation of lutein and zeaxanthin may benefit eye health. The National Eye Institute conducted a clinical trial, AREDS2, adding lutein and zeaxanthin to the AREDS1 supplement (consisting of β-carotene, vitamin C, vitamin E, zinc, and copper). The AREDS1 supplement lowered disease progression of AMD by 25% in a clinical trial (1). Adding lutein and zeaxanthin to the original AREDS1 supplement formulation lowered progression to advanced AMD by another 10%. β-Carotene supplementation was found to increase lung cancer incidence in former smokers, so investigators wanted to see if replacing β-carotene in the AREDS1 supplement with lutein and zeaxanthin would be an effective and safer alternative. It was concluded that replacing 15 mg of β-carotene in the supplement with 10 mg lutein and 2 mg zeaxanthin is a safe and beneficial modification, resulting in an additional 22% reduction in progression to advanced AMD. The AREDS2 study and other smaller-scale interventions did not show a protective effect for lutein and zeaxanthin in slowing the progression of cataracts.

Lutein and zeaxanthin preferentially accumulate in the brain and may play a role in cognitive health. Cognitive function is correlated with lutein and zeaxanthin plasma concentrations in healthy elderly adults (6). Higher concentrations are associated with improved cognitive function, while those with mild cognitive impairment and Alzheimer disease were depleted. MP, composed of lutein and zeaxanthin, is correlated with measures of cognitive function in healthy older men and women (6) and with concentrations in the brain in both humans and nonhuman primates (3). Therefore, MP may be a useful, noninvasive biomarker of lutein and zeaxanthin content in the brain. Although preliminary evidence for the role of lutein and zeaxanthin in cognitive health is encouraging, further large-scale clinical trials and interventions are needed to investigate their role.

Xanthophylls may be cancer preventative as scavengers of free radicals, quenchers of reactive oxygen species and reactive nitrogen species, and chain-breaking antioxidants. Astaxanthin is a potent antioxidant due to the 2 keto groups on its ring structure, and is thought to modify gap junction communication in cancer cells and alter inflammatory cancer pathways (7). The anticancer effects of lutein and zeaxanthin on breast cancer have recently been investigated and have produced conflicting data. A pooled analysis of 18 prospective cohort studies found that dietary intake of lutein and zeaxanthin was inversely associated with estrogen receptor (ER) negative (ER–) but not ER-positive (ER+) breast cancer (4). However, a more recent nested case-controlled study found no association between lutein or zeaxanthin serum levels and ER– or ER+ breast cancer (10). Serum levels may be a better indicator of usable carotenoids by the body compared to dietary collection methods, which are prone to reporter bias. Other factors, such as genetics, daily variation in blood concentrations, or interaction effects of other dietary components, may lead to conflicting results. Some suggest that high serum xanthophyll levels are a biomarker of fruit and vegetable intake, and thus the anticancer benefit may be the result of interactive effects of multiple components in fruits and vegetables (4, 10).

Oxidative stress and inflammation are key contributors to the development of cardiovascular disease, and xanthophylls, through their antioxidant or anti-inflammatory action, may reduce this risk. A recent systematic review with meta-analysis showed that higher lutein intake or serum concentration was associated with a lower risk of coronary artery disease (CAD) and stroke (5). Studies suggest that lutein may prevent arteriosclerosis and reduce inflammatory markers that may lead to cardiovascular disease. One study assessed the major carotenoids in human plasma and found that only lutein and zeaxanthin were inversely correlated to IL-6, an inflammatory biomarker of CAD, in patients with CAD (11). Peripheral blood mononuclear cells isolated from these patients and exposed to lutein resulted in a lower inflammatory response. Further studies are needed to clarify the role of xanthophylls in improving cardiovascular risk, but mechanisms may include vascular changes, antioxidant effects, or changes to the immune response or inflammation.

β-Cryptoxanthin may prevent bone loss by stimulating osteoblastic bone formation and inhibition of osteoclastic bone resorption (12). These effects were observed in vitro and are related to increased gene expression in proteins involved in bone formation. In vitro studies show that β-cryptoxanthin stimulates osteoclast cell death and suppresses gene expression of proteins involved in osteoclast bone resorption activity. β-Cryptoxanthin prevents bone loss in menopausal women, and epidemiologic studies indicate that it may reduce the risk of osteoporosis. The beneficial effect on bone health seems to be unique to β-cryptoxanthin and not to other carotenoids.

β-Cryptoxanthin has been studied for its use in the prevention and treatment of nonalcoholic fatty liver disease (NAFLD) (12). Nonalcoholic steatohepatitis is a more severe form of NAFLD, progressing to cirrhosis and hepatocellular carcinoma. β-Cryptoxanthin may halt progression from NAFLD to nonalcoholic steatosis by inhibiting lipid peroxidation and regulating macrophage formation.

Although not essential nutrients, xanthophylls may play important roles in health and disease. Since lutein and zeaxanthin preferentially accumulate in the brain and eye, future research will continue to focus on their mechanisms of function in relation to intake and disease prevention. As antioxidants, xanthophylls may prevent the development of cancer and cardiovascular disease. Future studies are needed to determine if these benefits are independent from or integrated with other nutrients in the diet. As the human lifespan increases, and with it the occurrence of chronic diseases, research into the prevention of disease by xanthophylls will likely continue.

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Abbreviations used: AMD, age-related macular degeneration; AREDS, Age-Related Eye Disease Study; CAD, coronary artery disease; ER, estrogen receptor; MP, macular pigment; NAFLD, nonalcoholic fatty liver disease.

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