NONVITAMIN AND NONMINERAL NUTRITIONAL SUPPLEMENTS

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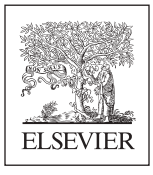

ACADEMIC PRESS

An imprint of Elsevier

Chapter 2.2

Astaxanthin, Lutein, and Zeaxanthin

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INTRODUCTION

Carotenoids are a group of natural, fat-soluble pigments produced by bacteria, algae, yeasts, fungi, and higher plants. Fish and crustaceans cannot synthesize carotenoids endogenously. However, they can absorb them from their diet and store them in their bodies (Rüfer et al., 2008).

Astaxanthin is the main carotenoid found in aquatic organisms such as salmon, shrimp, and lobsters. The chlorophyte algae *Haematococcus pluvialis* and the yeast *Phaffia rhodozyma* accumulate high levels of astaxanthin (Ambati et al., 2014). In addition, astaxanthin is related to other carotenoids such as zeaxanthin and lutein. These pigments share many metabolic and physiological functions attributed to carotenoids (Guerin et al., 2003).

Astaxanthin can act as an antioxidant, with more activity than other carotenoids (Campoio and Oliveira, 2011). The antioxidant activity of astaxanthin and other carotenoids is attributed to the oxygenated groups in each ring present in their structure (Fig. 2.2.1). Diverse clinical studies have reported that the intake of carotenoids can decrease the risk of macular degeneration, cancer, and heart disease, as well as protecting against diverse microbial infections (Lorenz and Cysewski, 2000).

Lutein and zeaxanthin are two very well-known antioxidant carotenoids present in the retina, which protect the eyes against inflammation and oxidative stress (Melo van Lent et al., 2016); these carotenoids are found in the human brain from the first year of life (Bovier et al., 2014). Recently, it has been reported that these compounds can inhibit lipid peroxidation in membranes and protect the skin against high energy sources (Juturu et al., 2016). Both compounds are present in high concentrations in egg yolk, fruit, and in leafy green vegetables (Kalariya et al., 2012).

Astaxanthin is safe when it is consumed with other food; to increase its biovailability it can be mixed with vegetable oils (Ambati et al., 2014). The main source of natural commercial astaxanthin is the microalga *H. pluvialis*, although synthetic astaxanthin is also available. Lutein and zeaxanthin supplements are produced from *Tagetes erecta* extracts (Juturu et al., 2016).

The astaxanthin-based supplements (Miyawaki et al., 2008; Park et al., 2010; Tominaga et al., 2012; Zanotta et al., 2014) zeaxanthin (Schwartz et al., 2016) and lutein (Zhang et al., 2017) used in clinical studies are produced and commercialized in different countries.

Diet and nutrition are important for maintaining health and preventing diseases; commercial dietary supplements are a source of essential nutrients. According to Block et al. (2007), dietary supplements containing the carotenoids lutein, zeaxanthin, astaxanthin, lycopene, and β-carotene are among the most highly consumed.

This chapter presents a detailed literary review of diverse human clinical trials involving the consumption of astaxanthin, lutein, and zeaxanthin as nutritional supplements, based on their biological properties and therapeutic value.

CHEMICAL STRUCTURE AND PROPERTIES

Astaxanthin, zeaxanthin, and lutein belong to the xanthophyll family of carotenoids. The presence of a terminal hydroxyl and ketones in the ionone rings underlies the esterification ability, antioxidant activity, and greater polar configuration of these compounds compared to other carotenoids. Carotenoids act as antioxidants by quenching singlet oxygen and free radicals (Campoio and Oliveira, 2011). The antioxidant activity of astaxanthin is 10-fold greater than the antioxidant activity of other carotenoids, such as zeaxanthin, lutein, canthaxanthin, and β-carotene, and 100–500-fold greater than the activity of α-tocopherol.

Nonvitamin and Nonmineral Nutritional Supplements. https://doi.org/10.1016/B978-0-12-812491-8.00003-5

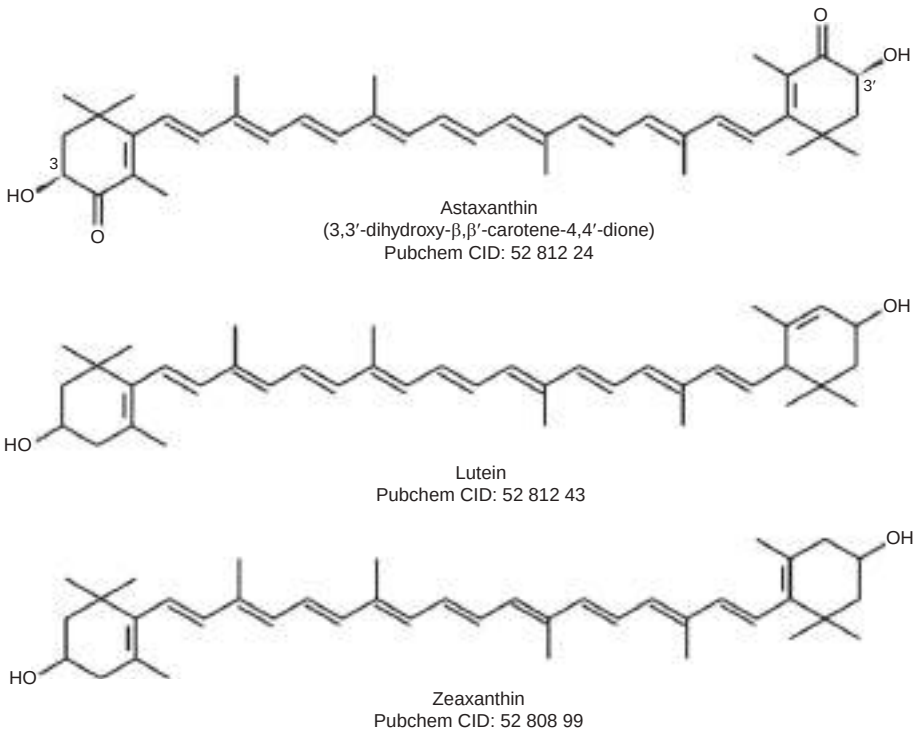

FIG. 2.2.1 Chemical structure of astaxanthin, lutein, and zeaxanthin.

Astaxanthin (3,3′-dihydroxy-β,β′-carotene-4-dione) is an oxycarotenoid; its name is derived from the crustacean *Astacus astacus*. This molecule is highly unsaturated and sensitive to high temperatures, light, and oxidative conditions that can cause the isomerization of astaxanthin to the *cis* form, which has lower activity than the *trans* configuration (Kittikaiwan et al., 2007). Because of the two stereogenic carbon atoms at positions C-3 and C-3′, astaxanthin exists in nature as a mixture of two enantiomers (3S, 3′S- and 3R, 3′R-astaxanthin) and a meso compound (3R, 3′S); the all-E-configuration is predominant (Grewe et al., 2007). Astaxanthin can exist in a free state or be esterified by fatty acids, forming monoesters and diesters (Núñez-Gastélum et al., 2016); it can also be associated with a protein, which is known as a caroprotein.

Lutein (β,ε-carotene-3,3′-diol) is a carotenoid belonging to the xanthophyll family (Kalariya et al., 2012). Its name is derived from the word *luteus*, meaning yellow. Structurally, lutein is comprised of a large carbon chain with a cyclohexenyl at each end containing a hydroxide group. The carbon chain has alternate double and single bonds, with lateral methyl groups (Kijlstra et al., 2012). Zeaxanthin (β,β-carotene-3,3′-diol), is a positional isomer of lutein. In both carotenoids, the hydroxyl groups allow orientation in cellular membranes and lipoproteins (Roberts et al., 2009).

NATURAL SOURCES

Astaxanthin

Astaxanthin is widely and naturally distributed in marine animals including, crustaceans, such as shrimp and crabs, and in fish such as salmon and trout (Yamashita, 2013). Astaxanthin and its esters have been isolated from the shells of lobsters (Maoka and Akimoto, 2008), river crabs (Meyers and Bligh, 1981), and shrimp exoskeletons (López-Cervantes et al., 2006; Sachindra and Mahendrakar, 2005). In crustaceans, astaxanthin accumulates primarily in the shell with its associated red–orange coloration only released following thermal or solvent treatment.

Astaxanthin is the main carotenoid in the microalga *H. pluvialis*, forming complex esters with several fatty acids. *Monoraphidium* sp., another microalga that produces astaxanthin, has a 10-fold greater concentration than *H. pluvialis* (Fujii et al., 2010). These microalgae could serve as continuous sources of astaxanthin following cultivation in large-scale bioreactors.

The red yeast, *P. rhodozyma*, is surprisingly different from other pigmented yeasts, because it synthesizes and accumulates astaxanthin as its main carotenoid pigment. The majority of astaxanthin produced is found in the free

form (Parajo et al., 1998). The astaxanthin concentration in *P. rhodozyma* ranges from 5 to 200 μg/g depending on the nutrients found in the growth medium (Johnson and Lewis, 1979). However, the highest astaxanthin yield produced by yeast is lower than levels found in microalgae, which are similar to those found in crustaceans.

Lutein and Zeaxanthin

Similar to other carotenoids, these two lipophilic pigments must be consumed in the diet because the human body cannot synthesize them. Lutein and zeaxanthin give egg yolks, animal fat, and the macula of the human retina their yellow color (Kalariya et al., 2012). Perry et al. (2009) determined that the main sources of lutein are spinach, cilantro, parsley, kale, unshelled pistachios, cooked egg yolk, and corn tortillas. They also reported that yellow corn flour, peppers, oranges, chives, and cooked egg yolks are sources of zeaxanthin.

BIOAVAILABILITY

Currently, only a few studies have examined the bioavailability of astaxanthin in humans. Carotenoids can be absorbed from the diet by passive diffusion into cells in the intestinal mucosa, where transportation is associated with plasmatic lipoproteins. Carotenoids have individual absorption patterns, metabolisms, and plasma transport mechanisms, all of which include geometric isomerization (Østerlie et al., 2000). Non-polar carotenoids (β-carotene and lycopene) are transported by low-density and very low-density lipoproteins; while polar carotenoids (zeaxanthin and lutein) are transported by low-density and high-density lipoproteins (Guerin et al., 2003). A considerable number of human studies have centered on the absorption, transport, and metabolism of carotenoids; however, limited information is available regarding xanthophylls.

Østerlie et al. (2000), investigated the distribution of astaxanthin isomers E/Z and R/Z in the plasma fractions and lipoproteins of three male subjects (aged between 37 and 43 years) following the ingestion of a 100-mg dose of astaxanthin. The maximum concentration of astaxanthin (1.3 mg/L) was reached at 6.7 h post administration and the half-life of astaxanthin was 21 h. Astaxanthin was found in very low-density lipoproteins (36%–64%), low-density lipoproteins (29%), and in high-density lipoproteins (24%). The isomer distribution of the lipoprotein fractions was not affected by time. The authors reported that astaxanthin from the diet was absorbed easily and incorporated into human plasma lipoproteins. In addition, they detailed the different capture mechanisms of astaxanthin E/Z isomers.

Because astaxanthin is a very lipophilic compound with low oral bioavailability, Mercke Odeberg et al. (2003) studied the bioavailability of astaxanthin in the presence of fats; the study included 23 healthy men aged between 20 and 46 years. All treatments included 40 mg of astaxanthin administered in one dose. Three formulations were prepared with different lipids and surfactant agents; the main source of astaxanthin in the formulations was the green microalga *H. pluvialis* as a powder rich in fats. Plasma concentrations were monitored throughout the assay and the absorption velocity of each formulation was evaluated. All formulations showed improved bioavailability; however, the formulation from glycerol monooleate and dioleate, with polysorbate-80 as the tensioactive agent, exhibited a 4-fold higher bioavailability than a commercial reference formulation.

In a recent study, Rüfer et al. (2008) examined the bioavailability and distribution of astaxanthin configuration isomers in human plasma following the ingestion of wild and cultivated salmon. The study involved 28 healthy men who consumed 250 g of wild or aquacultured salmon daily for 4 weeks. The level of the astaxanthin isomer standard in human plasma was found to be similar to that of the ingested salmon throughout the study. However, at day 28, the relative isomer proportion (3S, 3′S) was slightly higher and (3R, 3′R) was lower in human plasma than in the salmon meat. When participants were administered 1.25 mg of astaxanthin, the plasma concentration at day 3 ranged from 27.3 to 42.0 nmol/L. This result shows a nonlinear response to astaxanthin concentration in human plasma, possibly due to the saturation of absorption mechanisms and enterocyte transport at high doses.

ASTAXANTHIN IN HUMAN HEALTH

A series of studies have demonstrated that astaxanthin acts as a health promoter, specifically, in the prevention and treatment of cardiovascular, gastrointestinal, hepatic, neurodegenerative, ocular, and dermatological diseases, as well as diabetes, diabetic neuropathy, metabolic syndromes, cancer, and chronic inflammation (Yamashita, 2013). A number of human clinical studies are detailed in Table 2.2.1.

TABLE 2.2.1 Human Clinical Studies Using Astaxanthin as a Dietary Supplement

Reference/Study	Subjects and research design
Yoshida et al. (2010) Administration of natural astaxanthin increases serum HDL cholesterol and adiponectin in subjects with mild hyperlipidemia	Placebo-controlled study 61 nonobese subjects with moderate hypertriglyceridemia 0, 6, 12, and 18 mg/day of commercial astaxanthin for 12 weeks Aged between 25 and 60 years
Zanotta et al. (2014) Cognitive effects of a dietary supplement made from extract of *Bacopa monnieri*, astaxanthin, phosphatidylserine, and vitamin E in subjects with mild cognitive impairment: a noncomparative, exploratory clinical study	Prospective cohort, noncomparative, multicenter trial 104 subjects with minimental state One tablet daily containing astaxanthin (2 mg), vitamin E (30 mg), *Bacopa monnieri* dry extract (100 mg), and phosphatidylserine (30 mg) for a 60-day period Aged 71.2 ± 9.9 years
Katagiri et al. (2012) Effects of astaxanthin-rich *Haematococcus pluvialis* extract on cognitive function: a randomized, double-blind, placebo-controlled study	Randomized double-blind placebo-controlled study 96 healthy subjects One astaxanthin-rich capsule (6 mg/day or 12 mg/day) for 12 weeks Aged 55.7 ± 3.7 years
Kaneko et al. (2017) Protective effect of astaxanthin on vocal fold injury and inflammation due to vocal loading: A clinical trial.	10 nonsinger male subjects who consumed 24 mg/day of astaxanthin Aged between 23 and 30 years
Miyawaki et al. (2008) Effects of astaxanthin on human blood rheology	Single-blind method 10 adult men (57.5 ± 9.8 years) for a food study and 10 adult men (50.8 ± 13.1 years) for a placebo food study Two astaxanthin capsules once daily (6 mg astaxanthin/day) 10-day period
Tominaga et al. (2012) Cosmetic benefits of astaxanthin on human subjects	Two human clinical studies: Open label noncontrolled study with 30 healthy female subjects (aged between 20 and 55 years) for 8 weeks, 6 mg/day as oral supplement and 2 ml/day (78.9 μM/day) astaxanthin as topical application Randomized double-blind placebo-controlled study with 36 healthy male subjects (aged between 20 and 60 years) for 6 weeks, 6 mg/day as oral supplement
Park et al. (2010) Astaxanthin decreased oxidative stress and inflammation and enhanced immune response in humans	Double-blind placebo-controlled study 14 healthy female subjects (aged 20.2–22.8 years) 0, 2 or 8 mg/day astaxanthin for 8 weeks

Improvements in Memory and Learning

It is widely accepted that many people experience a gradual cognitive decline as they age (Zanotta et al., 2014). Brain health during mild cognitive decline, senile dementia, and Alzheimer's disease is related to oxidative stress. Katagiri et al. (2012) reported that the brain tends to produce reactive oxygen species (ROS) and free radicals when high levels of glucose and oxygen are consumed. Given these findings, it has been proposed that antioxidants protect the brain from ROS, thus maintaining mental health. Lobos et al. (2016) confirmed the neuroprotective effects of astaxanthin found in an in vitro model, showing that a daily intake of astaxanthin is a beneficial strategy for managing Alzheimer's disease and other neurological disorders.

Katagiri et al. (2012) studied the effect of an astaxanthin-rich extract (*H. pluvialis*) on the cognitive function of healthy middle aged and elderly subjects, with age-related forgetfulness, by evaluating cognitive performance. The CogHealth scores improved in the high-dosage group, while the Groton Maze Learning test scores improved in the low-dosage group. These results demonstrate that astaxanthin-rich extract from *H. pluvialis* can improve cognitive function in healthy individuals.

Zanotta et al. (2014) designed a clinical study to investigate the cognitive effect of a commercial phytotherapeutic supplement containing astaxanthin (*H. pluvialis*) in subjects diagnosed with mild cognitive decline. Participants were evaluated using the Alzheimer's Disease Assessment Scale cognitive subscale (ADAS-cog) and the clock drawing test. Both scores showed statistically significant improvement. Memory tests consisting of individual components of

the ADAS-cog showed greater improvement. The perceived efficacy was evaluated as excellent or good for 62% of the subjects in the study.

Amelioration of Dyslipidemia

The coexistence of hypertension, deficient tolerance to glucose, and dyslipidemia represent a known metabolic syndrome, which increases the risk for developing type 2 diabetes and cardiovascular diseases (Yamashita, 2013).

Yoshida et al. (2010) presented the first study regarding the effect of astaxanthin on the lipid profile of humans. Comparisons between the assays showed that 12–18-mg/day doses significantly reduced triglycerides and increased the adiponectin hormone content in serum. In addition, a 6–12-mg/day dose significantly increased high-density lipoprotein (HDL) cholesterol.

Protection of the Vocal Fold

Professionals using their voices excessively, such as singers, priests, and teachers, can develop vocal disorders with symptoms such as fatigue, lethargy, and dysphonia. Kaneko et al. (2017) designed a clinical study to evaluate the protective effect of astaxanthin on vocal fold lesions. These lesions are known to be aggravated by ROS generated by inflammatory cells. The results of the study showed that astaxanthin has the potential to protect mucous membranes against lesions and inflammation. The antiinflammatory effect of astaxanthin led to a significant improvement in the aerodynamics, acoustic function, and GRBAS (grade, roughness, breathiness, asthenia, strain) scale associated with the vocal fold. Astaxanthin can prevent scaring of the mouth fold by regulating oxidative stress during the early stages of cicatrization.

Relief From Eye Fatigue

Significant improvement in relief from eye fatigue has been observed following the ingestion of astaxanthin (Yamashita, 2013). In addition, promotion of visual fatigue or asthenopia recuperation has been shown to be attributable to improved blood circulation in the peripheral systems. Based on these findings, Miyawaki et al. (2008) studied the effect of a continuous ingestion of astaxanthin on blood rheology by conducting a test that measured the total time of blood transit using heparinized blood. A reduction in blood transit time, varying from 52.8 ± 4.9 s to 47.6 ± 4.2 s, was observed, thus confirming an improvement in blood rheology.

Recovery of Skin Elasticity and Recovery From Skin Dryness

A number of studies have examined the dermatological activity of astaxanthin. Tominaga et al. (2012) studied the cosmetic effects of astaxanthin based on two factors, administration technique and gender. They found that astaxanthin derived from *H. pluvialis* can improve the status of all skin layers by combining oral supplementation with topical treatment in both women and men.

Oxidative Stress, Inflammation, and Immune Response

Chronic inflammation is a determining factor for diseases such as hypertension, diabetes, and atherosclerosis (Kishimoto et al., 2016). In this study, the authors established that astaxanthin possesses preventive action against atherosclerosis due to its potential to improve inflammation, lipid, and glucose metabolism.

According to a hypothesis proposed by Park et al. (2010), astaxanthin, acting as an antioxidant and antiinflammatory agent, can improve the immune response. This study examined the immunostimulant, antioxidant, and antiinflammatory activity of astaxanthin in young, healthy women. The immune response was evaluated at week 0, 4, and 8, with a tuberculin test carried out on day 8. Depending on the concentration, plasma astaxanthin increased after week 4 and week 8. Subjects who received 2 mg of astaxanthin showed a higher tuberculin response than subjects with no supplementation. In general, this study demonstrated that astaxanthin can improve the immune response and decrease biological markers of DNA damage and inflammation in participants.

The levels of fatty acids in plasma can increase as a result of obesity, excessive exercise, and diabetes. In addition, the production of free radicals can increase in diabetic patients and thus generate conditions of oxidative stress. Given that fatty acids are instigators of oxidative stress, and astaxanthin has antioxidant activity, Campoio and Oliveira (2011) evaluated oxidative stress in human lymphocytes caused by a mix of fatty acids, as well as the protective action of astaxanthin using an in vitro assay. The results of the study showed that fatty acids can increase the production of superoxide anions, hydrogen peroxide, and nitric oxide. Additionally, astaxanthin decreased the production of ROS and the prolific growth of

cells treated with fatty acids. Lastly, the authors mentioned that astaxanthin partially prevents oxidative stress in human lymphocytes by controlling the production of free radicals.

THE ROLE OF LUTEIN AND ZEAXANTHIN IN HUMAN HEALTH

In adults, cognitive damage and dementia tend to increase with age. According to Johnson et al. (2008), this impairment in elderly individuals is related to a low consumption of lutein and docosahexaenoic acid (DHA). Based on the fact that lutein and DHA accumulate in the cellular membranes of the central nervous system, the authors designed a clinical assay to evaluate the effects of lutein and DHA in various cognitive domains in women (aged between 60 and 80 years). The participants received 12 mg of lutein or 800 mg of DHA, a mixture of both, or a placebo, daily for 4 months. The results demonstrated that verbal fluidity, memory, and processing speed improved significantly in patients who received lutein, DHA, or a mixture of both. These findings suggest that lutein and DHA improve cognitive function in elderly people.

It is well known that lutein is transported through a hematoencephalic barrier and accumulates in the macula of the retina and other nervous tissue. Based on previous findings, Bovier et al. (2014) hypothesized that an increase in lutein and astaxanthin concentrations in the visual system can improve visual processing speed. In this clinical study, the subjects (young men and women, aged between 18 and 32 years) were pooled in three groups to evaluate two commercial supplements and a placebo over a period of 4 months. One of the supplements contained zeaxanthin (20 mg) and the other zeaxanthin (26 mg) mixed with lutein (8 mg) and omega-3 fatty acids. Supplementation increased the concentration of macular pigment and improved visual processing speed.

CONCLUSIONS

This chapter reviewed astaxanthin, lutein, and zeaxanthin and has demonstrated that these natural carotenoids are bioactive compounds with biological activities than benefit human health. Currently, astaxanthin is the lipophilic pigment most widely used in clinical assays for disease prevention, based on its properties as an antioxidant and ameliorator of chronic inflammation. Specifically, astaxanthin, lutein, and zeaxanthin have shown effects against neurodegenerative, cardiovascular, and dermatological diseases. However, more clinical assays are required to warrant the protective effects and safe use of astaxanthin-, lutein-, and zeaxanthin-based dietary supplements.

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