Astaxanthin, Cell Membrane Nutrient with Diverse Clinical Benefits and Anti-Aging Potential

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Abstract

Astaxanthin, a xanthophyll carotenoid, is a nutrient with unique cell membrane actions and diverse clinical benefits. This molecule neutralizes free radicals or other oxidants by either accepting or donating electrons, and without being destroyed or becoming a pro-oxidant in the process. Its linear, polar-nonpolar-polar molecular layout equips it to precisely insert into the membrane and span its entire width. In this position, astaxanthin can intercept reactive molecular species within the membrane's hydrophobic interior and along its hydrophilic boundaries. Clinically, astaxanthin has shown diverse benefits, with excellent safety and tolerability. In double-blind, randomized controlled trials (RCTs), astaxanthin lowered oxidative stress in overweight and obese subjects and in smokers. It blocked oxidative DNA damage, lowered C-reactive protein (CRP) and other inflammation biomarkers, and boosted immunity in the tuberculin skin test. Astaxanthin lowered triglycerides and raised HDL-cholesterol in another trial and improved blood flow in an experimental microcirculation model. It improved cognition in a small clinical trial and boosted proliferation and differentiation of cultured nerve stem cells. In several Japanese RCTs, astaxanthin improved visual acuity and eye accommodation. It improved reproductive performance in men and reflux symptoms in *H. pylori* patients. In preliminary trials it showed promise for sports performance (soccer). In cultured cells, astaxanthin protected the mitochondria against endogenous oxygen radicals, conserved their redox (antioxidant) capacity, and enhanced their energy production efficiency. The concentrations used in these cells would be attainable in humans by modest dietary intakes. Astaxanthin's clinical success extends beyond protection against oxidative stress and inflammation, to demonstrable promise for slowing age-related functional decline.

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Introduction

Astaxanthin is a carotenoid nutrient with molecular properties that precisely position it within cell membranes and circulating lipoproteins, thereby imbuing them with potent antioxidant and anti-inflammatory actions.[1,2] Astaxanthin also effectively protects the double membrane system of mitochondria, to the point of boosting their energy production efficiency.[3] As a dietary supplement, astaxanthin demonstrates an exceptional range of benefits, mostly at very modest dietary intakes (40 mg/day or less). The molecular structure of astaxanthin is illustrated in Figure 1.

Humans do not make astaxanthin.[4] Current human dietary intake is almost exclusively from seafood. Astaxanthin is produced by algae, bacteria, and fungi, and concentrates higher up the food chain as these primary producers are consumed for food.[5] Its naturally intense red color brightens the flesh, skin, or exoskeleton of animals, such as crabs, crayfish, krill, lobsters, salmon, shrimp, and trout. It is also fed to farmed seafood for this coloring purpose. Astaxanthin also occurs naturally in flamingo feathers (where it is responsible for the characteristic color) and the retinas of quail.[6]

Although synthetic astaxanthin is available, it has a different molecular profile than the natural material, as do certain manufactured astaxanthin esters. This review is therefore restricted to natural astaxanthin, virtually all of which comes from commercial cultures of the single-celled alga *Haematococcus pluvialis (H. pluvialis)*.[7]

The clinical and basic science research on astaxanthin is considerable, although a number of the clinical trials in circulation were not published

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in peer-reviewed journals and some were published only in Japanese. However, the English-language, peer-reviewed publications sufficiently establish astaxanthin as a nutrient with broad-ranging efficacy and safety.

Biochemistry

The Unique Molecular Layout of Astaxanthin

Astaxanthin (3,3'-dihydroxy-beta,beta-carotene-4,4'-dione) belongs to the xanthophyll subclass of carotenoids. It has oxygen in its molecular structure, which sets it apart from beta-carotene and other molecules of the carotene subclass.[5] The astaxanthin molecule has an extended shape, with a polar structure at either end of the molecule and a nonpolar zone in the middle (Figure 1). The polar structures are ionone rings that have potent capacity for quenching free radicals or other oxidants, primarily in an aqueous environment, but possibly also in the absence of water.[8,9]

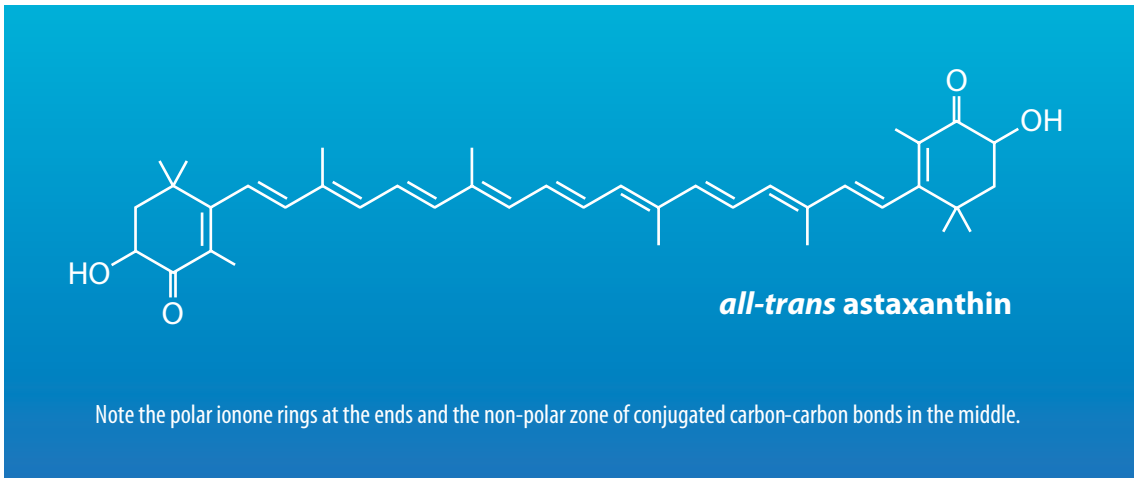
Complex Three-Dimensional Chemistry

The bonding patterns of natural astaxanthin generate many different molecular forms (isomers), each with its unique three-dimensional shape. The intricacies of astaxanthin's isomer array are beyond the scope of this review. Pertaining to its use as a dietary supplement, virtually all commercially available natural astaxanthin is predominantly in the *all-trans* geometric form 3S,3S' Astaxanthin, as occurs in *H. pluvialis* and as illustrated in Figure 1. This is the predominant natural astaxanthin used in all clinical trials to date.

Another complication in the chemistry of natural astaxanthin is that the molecule in its free form is relatively uncommon within the various organisms that produce it. Instead, most of this astaxanthin is either conjugated with proteins or esterified with one or two fatty acids (as astaxanthin acyl monoesters or diesters).[11] Acyl esters make up more than 99 percent of the astaxanthin from *H. pluvialis* and approximately 80 percent of astaxanthin in krill.[11,12] Thus, acyl monoester and diester forms make up virtually all the astaxanthin currently available in dietary supplements.

Key words: astaxanthin, antioxidant, carotenoid, cardiovascular, cell membranes, cognition, CRP, DNA damage, eye accommodation, free radicals, H. pylori, inflammation, immunity, male fertility, mitochondria, oxidative stress, redox, vision, xanthophyll

Figure 1. Molecular Layout of *All-trans* Astaxanthin, the Major Molecular Species in Natural Foods and Dietary Supplements



The nonpolar middle segment of the astaxanthin molecule is a series of carbon-carbon double bonds, which alternate with carbon-carbon single bonds – termed "conjugated." This series of conjugated double bonds gives the molecule a further antioxidant dimension, with a capacity to remove high-energy electrons from free radicals and "delocalize" their electronic energy via the carbon-carbon chain – analogous to a lightning rod on the molecular level (Figure 2).[10] This polar-nonpolar-polar layout also allows the astaxanthin molecule to take a transmembrane orientation, making a precise fit into the polar-nonpolar-polar span of the cell membrane.

Metabolism: Absorption and Tissue Distribution

In pharmacokinetic studies, after ingestion of esterified natural astaxanthin, only unesterified astaxanthin appears in the blood.[13] This is most likely due to breaking the ester bonds by digestive enzymes via their hydrolytic activity. Absorption into the intestinal lining cells (enterocytes) is thought to occur by passive diffusion and is

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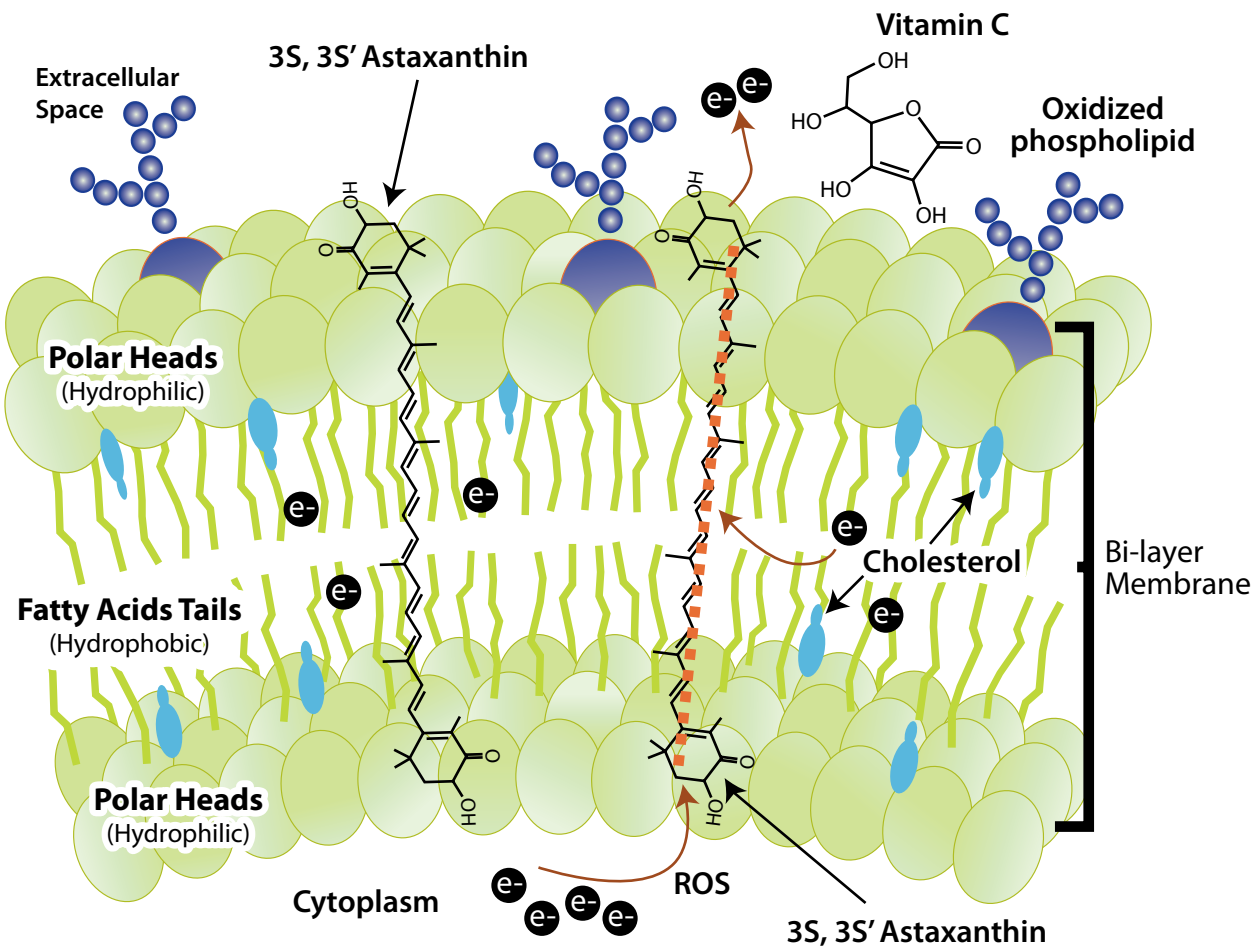
Figure 2. Transverse Cell Membrane Orientation of 3S,3S' Astaxanthin, the Major Molecular Form from H. pluvialis[10]



The polar end groups overlap the polar boundary zones of the membrane, while the nonpolar middle fits the membrane's nonpolar interior. The dashed red line speculatively indicates "lightning-rod" conduction of electrons along the astaxanthin molecule, possibly to vitamin C or other antoxidants located outside the membrane.

From: Pashkow FJ, Watumull DG, Campbell CL. Astaxanthin: a novel potential treatment for oxidative stress and inflammation in cardiovascular disease. *Am J Cardiol* 2008;101(suppl):58D-68D. Used with permission.

facilitated in the presence of fat or other lipids.[14] The enterocytes then incorporate the unesterified astaxanthin into chylomicrons, which transport it to the liver.[13] The liver does not convert this molecule to vitamin A or otherwise biochemically transform it.[4] Instead it becomes incorporated into low-density lipoprotein (LDL) and high-density lipoprotein (HDL), which then distribute it to the tissues via the circulation.[13]

When astaxanthin is fed to human subjects, detailed pharmacokinetic data are difficult to obtain for single doses of less than 10 mg, due to limitations of assay precision.[13] However, there is good data to indicate a single 10-mg dose can persist in the blood for 24 hours and a 100-mg dose for 76 hours.[13] Doses as low as 1 mg can significantly increase blood levels when taken once daily for four weeks.[15]

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Astaxanthin's bioavailability is substantially affected by meal timing and by smoking. In a 2009 study, a single 48-mg dose was much better absorbed when taken just after a meal than on an empty stomach, and was about 40-percent less bioavailable in subjects who smoked.[14]

Mechanisms of Action/Clinical Indications

A Unique Cell Membrane Antioxidant

Astaxanthin provides cell membranes with potent protection against free radical or other oxidative attack. Experimental studies confirm that this nutrient has a large capacity to neutralize free radical or other oxidant activity in the nonpolar ("hydrophobic") zones of phospholipid aggregates, as well as along their polar (hydrophilic) boundary zones.[5] A particularly elegant experimental study by McNulty et al conclusively established astaxanthin's membrane protection capacity.[1]

McNulty's group assembled model membranes from phosphatidylcholine and a small amount of cholesterol, at ratios similar to natural cell membranes.[1] They then introduced varying amounts of astaxanthin, zeaxanthin, lutein, beta-carotene, and lycopene to these model membranes and monitored the packing of the phospholipids by X-ray diffraction. They also induced peroxidative processes by gently increasing the temperature of the system. With the exception of astaxanthin, the carotenoids all disrupted the phospholipid packing *and* exacerbated peroxidative breakdown. The greater the membrane disruption by a carotenoid, the greater was its peroxidative effect. Only astaxanthin reduced peroxidation (by 41 percent) and preserved the membrane structure. The researchers gave particular credit to astaxanthin's unique ionone polar groups.

Astaxanthin's anti-peroxidative effect was evident in another study that had considerable social relevance.[16,17] In 2004, the pharmaceutical cyclooxygenase-2 (Cox-2) inhibitor rofecoxib was removed from commercial distribution due to its increased risk for atherothrombotic events.[16] It was found to increase the susceptibility of human LDL and cell membrane lipids to oxidative processes that contribute to atherosclerosis and thrombus formation. In a study using model lipid bilayers, rofecoxib caused peroxidative damage that was prevented by astaxanthin.[17] As found in the McNulty experiments,[1] astaxanthin switched the model membrane-carrying rofecoxib from net peroxidative balance to healthy anti-peroxidative balance.

Astaxanthin has also protected human LDL against oxidative attack. In a Japanese study,[2] astaxanthin purified from krill was provided to healthy volunteers (average age 28 years; n=24) at 0 mg/day, 1.8 mg/day, 3.6 mg/day, 14.4 mg/day, or 21.6 mg/day, for 14 days. After supplementation, venous blood was drawn and the LDL analyzed for susceptibility to oxidation (lag time after a chemical peroxidative trigger) for each subject compared to baseline. Astaxanthin significantly increased lag time, which indicated a protective effect, at the dose levels of 3.6 mg/day and higher.

Supplementation with astaxanthin may lower lipid peroxidation *in vivo*.[18] A double-blind, randomized, controlled trial (RCT) investigated astaxanthin (8 mg/day) versus a placebo for three months in Finnish men ages 19-33. Plasma 12- and 15-hydroxy fatty acids, both markers of lipid peroxidation, were statistically significantly reduced in the astaxanthin group (both with $p<0.05$), but not in the placebo group. The reduction in 15-hydroxy fatty acid in the astaxanthin group fell just short of significance when compared to the placebo group ($p=0.056$).

The membrane systems of cells are particularly vulnerable to free radical or other oxidative attack, owing to their content of polyunsaturated fatty acids and to their metabolic activities, which endogenously generate free radicals and other oxidants.[19] In its position spanning the membrane, astaxanthin provides versatile antioxidant actions, including:[1,8,9]

- donating electrons to unpaired electrons to neutralize free radicals;
- pulling away ("abstracting") an unpaired electron, which also can neutralize a radical;
- bonding with the radical to form an unreactive "adduct";
- conducting electrons or electronic energy out of the membrane (Figure 2);
- neutralizing radical species of nitrogen, sulfur, or carbon, in addition to oxygen; and
- carrying very low net molecular energy, therefore providing resistance to transformation into a pro-oxidant molecule.

Evidence of Antioxidant Effects in Clinical Trials

Significant antioxidant powers have been ascribed to astaxanthin, based primarily on experimental findings. The real breakthrough with this nutrient, however, is that it produces clinically significant antioxidant benefits in human subjects, including groups especially vulnerable to oxidative stress, such as smokers, the obese, and the overweight.

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Oxidative stress can be defined as a relative excess of free radical activity over antioxidant capacity, which in human subjects can be determined using blood samples.[20] Alternately, oxidative breakdown products can be measured in the blood.[21] People who are overweight or obese tend to manifest greater "oxidative stress" when compared to individuals within the normal weight range.[22] In a Korean double-blind RCT, astaxanthin "normalized" oxidative stress in individuals with weight challenges.[21]

In this three-week study, overweight and obese individuals (body mass index [BMI] >25.0 kg/m^2; n=23) were randomized to receive astaxanthin at 5 mg/day or 20 mg/day and compared to a control group (n=10) with normal body weight (BMI <25.0 kg/m^2) who received no intervention.[21] At baseline, the plasma levels in overweight and obese individuals were significantly higher than normal weight individuals on two oxidative biomarkers – malondialdehyde (MDA) and isoprostanes (ISP), while plasma levels in overweight and obese individuals were significantly lower on two antioxidant measures – superoxide dismutase (SOD) and total antioxidant capacity (TAC). At the three-week mark, when compared against baseline, both astaxanthin groups showed significant lowering of oxidative markers MDA ($p<0.01$ for both groups) and ISP ($p<0.01$ for 5 mg/day; $p<0.001$ for 20 mg/day). The astaxanthin groups also had significant increases in SOD and TAC (all $p<0.001$ versus baseline). Marked improvements on all four measures caused the overweight and obese subjects to become statistically indistinguishable from the control group, suggesting that supplementation lowered oxidative stress and improved aspects of the antioxidant defense system. The improvements were not significantly better for the 20 mg/day group than the 5 mg/day group.

In another RCT conducted by the same group, and made available as an electronic summary pending publication (September 2011),[23] heavy smokers (n=39) were randomly allocated to receive astaxanthin at 5-, 20-, or 40 mg/day for three weeks. Compared with baseline, the plasma MDA and ISP levels decreased, whereas SOD level and TAC increased in all intervention groups over the three-week period. In particular, ISP levels showed a significant dose-dependent decrease after astaxanthin intake.

Astaxanthin also can protect against oxidative DNA damage. In a 2010 double-blind RCT conducted by Park et al,[24] healthy women (ages 20-23; n=42) received either a placebo or astaxanthin at doses of 2 mg/day or 8 mg/day for eight weeks. Both astaxanthin dosages significantly lowered plasma 8-hydroxy-2'-deoxyguanosine (8-OHdG), an indicator of oxidative DNA breakdown. Plasma 8-isoprostane, a marker of lipid peroxidation, was not significantly lowered. The authors attributed this finding to a lack of sensitivity and accuracy in their assay method.

Anti-inflammatory Benefits

In the Park double-blind RCT,[24] astaxanthin also significantly lowered C-reactive protein (CRP), a biomarker of systemic inflammation.[25] Although the 2-mg/day dose had a significant CRP-lowering effect, the 8-mg/day dose fell short of statistical significance. Compared with the lower dose, the 8-mg/day dose significantly increased the cytokine interferon-gamma, which may indicate an anti-inflammatory effect, but also significantly increased interleukin-6 (IL-6), which can have a pro-inflammatory effect. The clinical significance of these findings is unclear, particularly since none of these, except CRP, is a generally accepted inflammatory marker.

Astaxanthin's effect on CRP was also investigated in a small double-blind trial that was published without peer review.[26] Subjects (ages 40-60 years; n=19), with no diagnosis of cardiovascular disease, kidney disease, diabetes, or cancer, received three softgel capsules daily supplying either astaxanthin at 12 mg/day (with 120 mcg of lutein, 195 IU of vitamin A activity [in the form of beta-carotene), and 150 IU of vitamin E) or a placebo (safflower oil) for eight weeks. The astaxanthin combination lowered CRP levels by about 20 percent (from 1.35 mg/dL to 1.07 mg/dL), which was significantly better than placebo ($p<0.05$).

An eight-week, double-blind RCT conducted on rheumatoid arthritis subjects was published in abstract form.[27] One group (n=14) received the same combination as in the previously described study – 12 mg/day astaxanthin plus 120 mcg of lutein, 195 IU vitamin A activity (from beta-carotene), and 150 IU of vitamin E, while the other group (n=7) received a placebo. The improvement in self-reported scores of pain and satisfaction for the astaxanthin group was significantly better than for the placebo group, which suggests a possible anti-inflammatory effect.

Astaxanthin has been reported to benefit other inflammatory conditions such as canker sores, carpal tunnel syndrome, and "tennis elbow," but the evidence currently available to support these claims is insufficient.

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Promotes Integrated Immune Response

The Park double-blind RCT investigated astaxanthin most extensively for its immune system benefits over the eight-week trial period.[24] At the 2-mg/day dose, total T- and B-cell numbers were significantly increased over placebo ($p<0.05$ for both comparisons). At the 8-mg/day dose, natural killer cell cytotoxic activity increased, as did lymphocyte proliferation in response to mitogen stimulation ($p<0.05$ for both comparisons). Skin delayed-type hypersensitivity (DTH), an excellent measure of integrated cell and humoral mediated immunity, was significantly improved by the 2-mg/day dose ($p<0.05$). The researchers concluded astaxanthin promotes overall immune competence.

Astaxanthin was also tested for skin immunity in another double-blind RCT.[7] Patients (ages 19-51 years; n=27) with mild-to-moderate atopic dermatitis received either 12 mg/day astaxanthin or a placebo for four weeks. Although astaxanthin did not significantly improve the dermatitis severity, a significant shift in T-helper1/T-helper2 (Th1/Th2) balance was observed – with a shift toward Th1 dominance. The researchers judged this an important finding since atopic dermatitis is considered a Th2-dominant disease. Those in the astaxanthin group also experienced significant improvement in anxiety and other quality of life symptoms compared to placebo.

Effects on Metabolic Syndrome

Astaxanthin improved certain blood lipids in subjects with moderately elevated serum triglycerides (TGs). Healthy non-obese subjects (BMI <28 kg/m^2), ages 20-65 years (n=61) with fasting TGs in the range 120-200 mg/dL, were recruited into a double-blind RCT.[28] They were randomly allocated to receive astaxanthin at 6 mg/day, 12 mg/day, or 18 mg/day, or a placebo for 12 weeks. Astaxanthin, as compared to placebo, significantly elevated HDL-cholesterol at the doses of 6 mg/day ($p<0.05$) and 12 mg/day ($p<0.01$). It also significantly lowered TGs at doses of 12 mg/day and 18 mg/day ($p<0.05$ for both) compared to placebo. There was no effect on LDL-cholesterol at any dose. Astaxanthin also significantly increased blood adiponectin levels ($p<0.01$ at 12 mg/day; $p<0.05$ at 18 mg/day).

Adiponectin is a hormone produced by adipose tissue, cardiac and skeletal muscle, and vessel endothelia. Serum levels of adiponectin tend to be reduced in obese and/or diabetic subjects, smokers, patients with coronary heart disease, and individuals with metabolic syndrome.[29] Although the results of this study suggest a normalization of adiponectin levels, 12 weeks of supplementation had no effect on BMI.

In a small, open-label trial (16 subjects), astaxanthin did not produce clinically significant benefits on any of the criteria for metabolic syndrome.[30] Further investigation is required under better-controlled conditions in order to clarify astaxanthin's utility for this condition.

Effects on Circulation

As people age, their red blood cells (RBCs) can be more susceptible to oxidative attack, resulting in peroxidative damage to the RBC membrane phospholipids,[31] impairing its oxygen-carrying capacity. In a 2011 double-blind RCT,[32] healthy subjects, ages 50-69 years (n=30), were randomly allocated to receive astaxanthin at 6 mg/day or 12 mg/day or a placebo for 12 weeks. Both astaxanthin intakes significantly lowered RBC hydroperoxide levels ($p<0.05$ for both doses versus placebo); the 12 mg/day dose did not work significantly better than the 6 mg/day dose.

Astaxanthin also improved an experimental measure of "rheology" (blood flow capacity) in healthy men.[33] Venous blood was drawn with heparin to protect against coagulation, then forced using mild pressure through tiny "microchannels," each just seven millionths of a meter wide, approximating the diameter of an RBC and the width of a capillary. The time required to traverse these capillary-type tubes under a set pressure was termed the transit time. A total of 20 men were selected whose blood demonstrated transit times in the range of 45-70 seconds per 100 microliters. They were then randomly allocated to receive either astaxanthin (6 mg/day) or a placebo for 10 days. Upon retest, the astaxanthin group had significantly faster transit time ($p<0.05$) compared to placebo. This finding suggests astaxanthin could potentially improve microcirculation.

Preliminary Benefits for Memory and other Higher Brain Functions

Astaxanthin might improve cognitive functions. In a small, open-label trial, 10 healthy men ages 50-69, who had been complaining of forgetfulness, received astaxanthin (12 mg/day) for 12 weeks.[34] On a computerized test designed to accurately detect early cognitive deterioration ("CogHealth" from CogState Ltd, Melbourne, Australia),[35] they showed improvement on measures of reaction time, attention, and working memory.

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Although this trial clearly was only preliminary, astaxanthin has shown a variety of brain benefits under experimental conditions. Unlike much of the experimental research conducted with this nutrient, the following studies employed levels readily achieved by oral intake in humans. Astaxanthin:

- significantly improved the memory performance of mice in the Morris water maze;[36]
- effectively protected cultured nerve cells against hydrogen peroxide toxicity,[37,38] and down-regulated genes linked to cell death and up-regulated genes linked to cell survival;[38]
- specifically protected the mitochondria of cultured nerve cells against toxic attack;[3,37,38] and
- stimulated the proliferation of cultured nerve stem cells.[39]

Effect on Vision and Eye Fatigue

Astaxanthin has been extensively researched for its benefits for vision, especially in Japan. Yuan[11] and Kajita (2009)[40] discussed double-blind and other controlled trials that were published in Japanese with English abstracts. They concluded that astaxanthin taken at 6 mg/day consistently improved visual sharpness, even in healthy subjects.

Astaxanthin also might relieve eye fatigue in persons using computer monitors. Extended work at computer monitors is linked to eyes strain and to blurred vision, often accompanied by tensing of the muscles of the shoulder and low back.[41] One double-blind RCT used instrumentation to measure eye muscle endurance, the usual basis for eye strain.[42] Japanese visual display terminal (VDT) workers, ages 38-53 (n=26), received astaxanthin (5 mg/day) or a placebo for four weeks. A non-VDT control group received neither astaxanthin nor placebo. After supplementation, eye strain was significantly more improved in the astaxanthin group than in the placebo group ($p<0.05$).

Many individuals, as they age, suffer decline in the eye's ability to focus on near objects (presbyopia). In an open-label Japanese trial,[40] papillary constriction capacity was determined using instrumentation in presbyopic middle-aged and older subjects (ages 46-65 years; n=22). They then received astaxanthin (6 mg/day) for four weeks. Astaxanthin significantly improved pupillary constriction, and more than 60 percent of the subjects indicated on a questionnaire that they also experienced improvement in the categories of "difficulty to see near objects," "eye strain," "blurred vision," and "shoulder and low-back stiffness."

Muscle Performance and Endurance

In a double-blind RCT,[43] young healthy male students (ages 17-19 years; n=40) were subjected to fitness, strength, and endurance testing, then randomized to receive astaxanthin (4 mg/day) or a placebo for six months. Astaxanthin significantly improved performance in the assessment designed to measure strength/endurance (maximum number of knee bends ["squats"] performed while carrying a 42.5 kg barbell) over the placebo group ($p<0.05$). The maximum number of knee bends increased by more than 50 percent in the astaxanthin group versus 19 percent in the placebo group. No benefit was detected for the assessments of strength/explosivity or overall fitness. This finding (and probably others asserted from unpublished trials) may have motivated the double-blind trials currently in progress with astaxanthin for protection against oxidative stress[44] and for improving speed and endurance in soccer players.[45]

Effect on *Helicobacter pylori* in Functional Dyspepsia

In a 2008 RCT, astaxanthin was evaluated for functional dyspepsia (FD).[46] Patients with FD (ages 18-70 years; n=130) were screened by detailed questionnaires, gastroscopy, and urea breath test for *H. pylori*. Of the 130 total patients, 81 (62%) tested positive for *H. pylori*. All patients were then randomized to receive, in double-blind fashion, astaxanthin at 16 mg/day or 40 mg/day or a placebo for four weeks. Gastrointestinal symptoms were measured using the Gastrointestinal Symptom Rating Scale (GSRS) to assess abdominal pain, indigestion, and reflux; quality of life was assessed using the SF-36 questionnaire. Treatment lasted four weeks, with a follow-up after another four weeks.

At the end of therapy (week 4), a strong placebo effect was evident, and there was no significant difference among the three treatment groups for GSRS scores of abdominal pain, indigestion, and reflux syndromes; the same results were observed at the end of follow-up. The researchers concluded astaxanthin did not have a global curative effect on FD. However, the higher dose of astaxanthin (40 mg/day) did significantly reduce symptoms associated with acid reflux, compared to the 16-mg/day dose and the placebo ($p<0.05$ for both comparisons).[46] The high-dose astaxanthin also significantly improved well-being in this group, as judged from the health transition item on the SF-36 quality of life questionnaire ($p<0.05$ for both comparisons).

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Subgroup statistical comparisons of the *H. pylori*-positive patients versus the *H. pylori*-negative patients revealed that the high-dose astaxanthin benefited reflux syndrome significantly better than placebo ($p<0.05$) only in the patients positive for *H. pylori*. The researchers speculated that astaxanthin helped suppress the elevation of oxidative stress associated with *H. pylori* infection.

Another smaller double-blind RCT, conducted by this same group, assessed astaxanthin for gastric inflammation in patients with FD.[47] Patients (n=44) were randomized to receive either astaxanthin (40 mg/day) or a placebo for four weeks, with a follow-up after another four weeks. Endoscopy was used to obtain gastric antral biopsies, which were then histologically scored for gastritis morphology. Histology was also used to score *H. pylori* density and for immunostaining to detect interleukin cytokines as well as cell surface immune markers. The researchers found that patients without *H. pylori* had no or only mild chronic inflammation, whereas patients with *H. pylori* had mild, moderate, and severe chronic inflammation in addition to no, mild, or moderate active gastritis.

The data from this trial for astaxanthin compared to placebo were inconclusive.[47] No significant changes were reported for the *H. pylori*-negative patients. In those patients with *H. pylori*, inflammation was significantly decreased after taking either astaxanthin or placebo, with no significant superiority of astaxanthin over placebo. The biopsies from these patients also showed no significant changes in density of *H. pylori* or in any of the interleukins. The researchers reported that in the *H. pylori* patients, astaxanthin significantly up-regulated CD4 lymphocytes ($p<0.05$) and significantly down-regulated CD8 lymphocytes ($p<0.01$), while the placebo significantly down-regulated CD4 and significantly up-regulated CD8. However, they did not provide sufficient statistical data to confirm any difference between astaxanthin and placebo.

Male Fertility and Reproduction

In a double-blind RCT, astaxanthin was evaluated for protecting sperm function and fertility.[48] Thirty men were recruited, all from infertile couples in which the female partner showed no demonstrable cause of infertility. They were randomized to receive either astaxanthin (16 mg/day) or a placebo for three months. During that period they were allowed to provide semen for intrauterine insemination, and pregnancy occurrence was recorded.

By the end of three months, sperm linear velocity was significantly increased in the astaxanthin group ($p<0.05$) but not in the placebo group.[48] Semen oxygen radical generation (upon stimulation by the oxidant phorbol ester) was markedly decreased in the astaxanthin group ($p<0.05$). However, the most telling outcome of this trial was the pregnancy rate, which was 54.5 percent for the astaxanthin group compared to 10.5 percent for the placebo group ($p<0.05$).

Effect on Mitochondrial Function

The mitochondria have double membranes crammed with catalytic proteins that utilize oxygen to generate energy;[16] however, a small proportion of this oxygen escapes catalytic control and is transformed into electronically excited reactive oxygen species (ROS). Some of these are neutralized by the antioxidant defenses, but others evade neutralization and pose a threat to the mitochondrial membranes.[49] Mitochondrial decline due to cumulative ROS damage has been suggested as contributing to the aging process.[50]

In a series of experiments with various cultured cell lines,[3] astaxanthin improved cell survival under oxidative stress (from the addition of antimycin A, which increases mitochondrial ROS generation). By adding an oxidant-sensitive molecular probe into the mitochondria, the researchers found that astaxanthin reduced the mitochondria's endogenous production of oxygen radicals and protected the mitochondria against a decline of membrane function that typically occurs over time in these cultures. Astaxanthin's positive activity went even further; it increased mitochondrial activity in these cells by increasing oxygen consumption without increasing generation of ROS.

The researchers then inserted into the mitochondria another molecular probe that measured their reducing or redox activity, which mirrors their capacity to conserve glutathione and re-reduce oxidized biomolecules.[3] The mitochondria were then challenged with hydrogen peroxide (H_2O_2), an ROS that should normally oxidize and reverse this redox state. Astaxanthin was found to protect against the H_2O_2 oxidant effect. The concentrations of astaxanthin required for these *in vitro* effects (100-800 nM/L) are achievable in humans by dietary supplementation.[30,51] Its capacities both to protect mitochondria and to boost their energy efficiency should stimulate further research into this nutrient's potential for possible anti-aging effects.

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Safety/Toxicity

Astaxanthin has demonstrated safety in numerous human clinical trials. In one open-label clinical study on subjects with metabolic syndrome (n=17),[30] astaxanthin (16 mg/day, for three months) significantly raised blood bilirubin ($p \leq 0.05$), potassium ($p \leq 0.05$), and creatine kinase ($p \leq 0.01$), although all three values remained within normal range. Also, astaxanthin significantly lowered the liver enzyme gamma-glutamyl transpeptidase (GGTP; $p \leq 0.05$). Since the researchers noted this enzyme was abnormally elevated in 11 of the 17 subjects at baseline, this astaxanthin effect may have been beneficial.

Animal experiments have investigated astaxanthin at levels well over 120 mg/day in human equivalents,[52] without causing apparent harm. Hoffman-La Roche confirmed its safety with extensive tests, including acute toxicity, mutagenicity, teratogenicity, embryotoxicity, and reproductive toxicity.[53]

Suggested Dosage

The doses of astaxanthin used in clinical trials have ranged from 1 mg/day to 40 mg/day (with the majority in the 6-12 mg range); single-dose pharmacokinetic studies used up to 100 mg per dose. As a dietary supplement, astaxanthin should be taken along with fats, with or immediately prior to meals, to ensure its optimal absorption.[51]

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