

Astaxanthin a poly-crest Remedy: Evidence-based Review on Action and Effects focused on clinical trials

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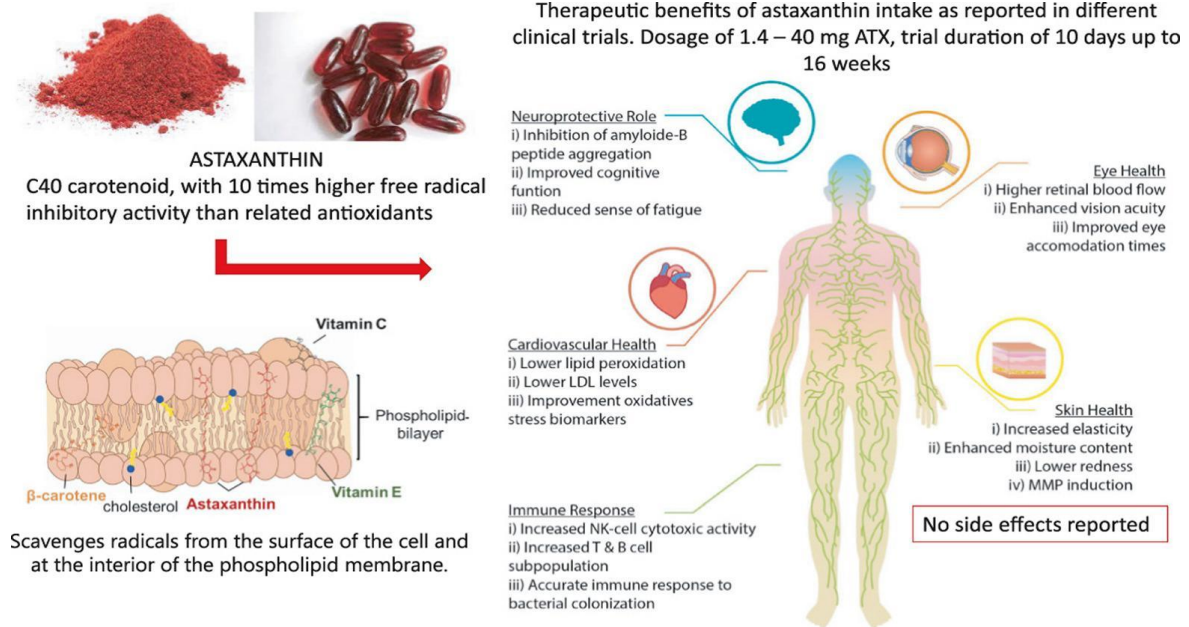
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Abstract: Astaxanthin is a type of carotenoid, which is a natural pigment found in a variety of foods. In particular, this beneficial pigment lends its vibrant red-orange colour to foods like krill, algae, salmon and lobster. Astaxanthin is an antioxidant. This effect might protect cells from damage. Astaxanthin also improves the way the immune system functions. *In vitro* and *in vivo* studies have associated astaxanthin's unique molecular features with several health benefits, including neuroprotective, cardioprotective and antitumoral properties, suggesting its therapeutic potential for the prevention or co-treatment of dementia, Alzheimer, Parkinson, and cardiovascular diseases. Focusing on human clinical trials, including a brief description of the potential mechanisms of action responsible for its biological activities. It is potentially used for the prevention of skin anti-ageing and the treatment of eye diseases like glaucoma. In this review, we summarise and discuss the currently available evidence on astaxanthin benefits,

Keywords: Astaxanthin, immune system functions, cardiovascular diseases, eye diseases like glaucoma.

1. INTRODUCTION

The astaxanthin molecule has two asymmetric carbon atoms at positions 3 and 3'. In nature, isomers with a chirality 3S, 3'S, or 3R, 3'R are the most abundant, among which, the former has the highest reported antioxidant activity. Synthetic astaxanthin consists of a combination of 3R,3'R; 3R, 3'S. Astaxanthin contains conjugated double bonds, hydroxyl, and keto groups, showing both lipophilic and hydrophilic properties. The conjugated double bonds at its centre are responsible for its red colour and, most important, for its high antioxidant capacity, as it donates the electrons that react with free radicals to convert them into more stable products, blocking free radical chain reactions. As astaxanthin shows both lipophilic and hydrophilic properties, this molecule is exposed to both the inside and outside of the cell, where it can scavenge radicals from the surface of the cell and at the interior of the phospholipid membrane. Indeed, studies have demonstrated that astaxanthin shows the highest antioxidant activity when compared to related carotenoids, being 10 times stronger. The research studied the scavenger effect of astaxanthin and related carotenoids (zeaxanthin, lutein, canthaxanthin and β -carotene) against free radicals, using the thiobarbituric acid reactive substances (TBARS) assay with α -tocopherol as control. The results showed that astaxanthin has the highest scavenger effect, with an ED50 of approximately 200 nM, whereas other carotenoid samples were in the range of 200–1000 nM. *In vivo*, assays carried out in the same study also demonstrated that astaxanthin shows the lowest ED50 values (2 μ M) when assessing its inhibitory activity against the action of free radicals on rat blood cells and mitochondria. More specific fluorometric assays, based on BODIPY fluorescent probes that are susceptible to oxidation by peroxy radicals, have also demonstrated that astaxanthin shows the highest relative antioxidant activity (1.3 ± 0.2) when compared to the antioxidant Trolox (1.0) and the carotenoids α -tocopherol (0.9), α -carotene (0.5), β -carotene (0.2), lutein (0.4) and lycopene (0.4). Carotenoids have gained special interest during the last decades, due to their strong antioxidant, repairing, antiproliferative, anti-inflammatory, and potential anti-ageing effects. They can be used to prevent oxidative stress-related diseases and chronic inflammation. Astaxanthin is one of the most powerful carotenoids on the market. In this review, a special focus is oriented towards these compounds.



2. ASTAXANTHIN: A SPECIAL CAROTENOID

Carotenoids, the precursors of vitamin A, are natural pigments supplied with regular highly conjugated π -bond systems, providing the natural yellow, orange, or red colours of many vegetables and fruits. Since the structural elucidation of β -carotene by the two scientists Kuhn and Karrer in 1930, more than 750 naturally occurring carotenoids have been reported to date.

Based on their structure, carotenoids can be compiled into two main groups:

- (i) The carotenes, also called carotenoid hydrocarbons, only contain carbon and hydrogen
- (ii) the xanthophylls or oxygenated carotenoids that may contain different functional groups (epoxy, methoxy, hydroxy, carbonyl, and carboxylic acid groups).

The most notable carotenoid, β -carotene, another carotenoid has been receiving great attention lately: astaxanthin, a marine xanthophyll carotenoid first isolated from a lobster by Kuhn and Soerensen. Astaxanthin is extensively produced by algal species such as *Haematococcus pluvialis* (where it accumulates up to 3.8% on the dry weight basis), *Chlorella zofingiensis*, and *Chlorococcum* and also by the yeast *Phaffia rhodozyma*. Astaxanthin confers the rich pink colour observed in various aquatic species including the salmonids and crustaceans and even some non aquatic species such as the flamingo. Sea creatures cannot produce astaxanthin themselves and must obtain it from their diets, which include zooplankton and krill. Krill oil contains appreciable content of astaxanthin at 0.1 to 1.5 mg/mL depending on processing methods. Krill oil is a superior source of EPA (eicosapentaenoic acid) and DHA (docosahexaenoic acid) which are both long-chain omega-3 fatty acids because the polyunsaturated fats are packaged as phospholipids, which ultimately can be used instantly by our body.

Astaxanthin is a fat-soluble nutrient (it incorporates into cell membranes) with increased absorption when consumed with omega-3-rich seed oil; however, it cannot be converted to vitamin A and therefore cannot support retinol-specific processes such as vision. With its unique molecular structure, astaxanthin stretches through the bilayer membrane, providing resilient protection against oxidative stress. It can scavenge and quench ROS and free radicals (superoxide anion, hydrogen peroxide, singlet oxygen, etc.) in both the inner and outer layers of the cellular membrane unlike most antioxidants, which work either in the inner (e.g., vitamin E and β -carotene) or the outer side of the membrane (e.g., vitamin C). Astaxanthin derived from the microalgae *H. pluvialis* has been approved as a colour additive agent in salmon feeds and as a dietary supplement for human consumption for more than 20 years in dosages up to 12 mg per day and up to 24 mg per day for no more than 30 days in Europe, Japan, and the USA.

3. EFFECTS ON INFLAMMATION AND CVD

The importance of oxidative stress and inflammation in atherosclerotic plaque development and cardiovascular disease progression is well known. low-density lipoprotein cholesterol oxidation represents the first step of initiation and

progression of atherosclerosis, in the setting of a global inflammatory process including oxidative stress, endothelial dysfunction, and vascular remodelling.

On the basis of the close interrelationship between oxidative stress, inflammation, and atherosclerosis, several studies have been performed to investigate the benefits of nutrients and food components with known antioxidant effects on cardiovascular health. The antioxidant properties of vitamins C, E, and A seemed to be effective against different conditions able to promote cardiovascular disease, that is, high blood pressure, impaired glucose and lipid profile, and smoke abuse, with a positive influence on every step of atherosclerotic progression (endothelial dysfunction, low-density lipoprotein cholesterol oxidation, monocyte, and smooth muscle cell activity). Nevertheless, even more important is the role of carotenoids.

In fact, it showed to have the highest antioxidant activity toward peroxy radicals among lutein, lycopene, α -carotene, β -carotene, α -tocopherol, and 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid. Astaxanthin demonstrated to exert beneficial effects on the heart both by reducing inflammation associated with atherosclerosis and by modifying blood levels of LDL-C and HDL-C, moreover, it showed to significantly reduce macrophage infiltration and apoptosis in vascular lesions improving plaque stability by increasing adiponectin.

4. EFFECT ON ANTIOXIDANT

Cell membrane systems are particularly vulnerable to RONS attacks due to their content of polyunsaturated fatty acids (PUFAs) and their metabolic activities, which endogenously generate other oxidising metabolites. Astaxanthin protects cell membranes against RONS and oxidative damage. Due to its chemical structure, its polar groups overlap the polar regions of the cell membrane, while the central nonpolar region of the molecule fits into the inner nonpolar region of the membrane. Thus, this carotenoid may take on a transmembrane alignment in biological membranes, helping to maintain the membrane structure and decrease membrane fluidity, and act as an antioxidant.

Astaxanthin scavenges RONS and other reactive species (sulphur and carbon) directly, both by donating electrons and by bonding with the free radical to form a non-reactive product. In addition, the presence of a series of conjugated bonds in the central nonpolar region of astaxanthin enables the molecule to remove free radicals (high-energy electrons) from the cell interior by transporting them along its own carbon chain, resembling a 'lightning rod' for these electrons, so that these are neutralised by other antioxidants located outside the cell membrane, such as vitamin C.

The increased susceptibility of membrane lipids and low-density lipoprotein (LDL) to oxidation may trigger the formation of thrombi and the development of atherosclerosis. One of the reactive species that induces lipid peroxidation and LDL oxidation is peroxynitrite (ONOO^-), which is neutralised by astaxanthin to form 15-nitro astaxanthin, a compound that also has important antioxidant action.

The LDL oxidation time in the presence of astaxanthin has been analysed *in vitro* and *ex vivo*. In the *in vitro* assays, astaxanthin prolonged LDL oxidation in a dose-dependent manner, in addition to being more effective compared with lutein and α -tocopherol. In turn, the blood samples of individuals who were supplemented daily with 1.8, 3.6, 14.4, or 21.6 mg astaxanthin for 14 days evidenced a significant delay in LDL oxidation when compared to samples collected before supplementation, the greatest effect being obtained with the dose of 14.4 mg (oxidation time increased by 5.0, 26.2, 42.3 and 30.7% with 1.8, 3.6, 14.4 and 21.6 mg astaxanthin, respectively). Thus, it was demonstrated that the intake of astaxanthin delayed LDL oxidation, one of the key factors involved in the process of atherosclerosis.

| Study type | Subjects (age) | Intervention (no. of subjects per group) | Mechanism of action evaluated | Main findings |
|--|--|--|-------------------------------|--|
| Open-label | 24 healthy volunteers (mean, 28.2±7.8 years) | Control (n=6); AST 1.8 mg/day (n=5); AST 3.6 mg/day (n=5); AST 14.4 mg/day (n=3); AST 21.6 mg/day (n=5); 14 days | Antioxidant effect | Delayed LDL oxidation time |
| Randomized, double-blind, placebo-controlled | 27 overweight and obese adults (BMI>25 kg/m ²) (20-55 years) | Placebo (n=13); AST 20 mg/day (n=14); 12 weeks | Antioxidant effect | Reduced LDL, ApoB and ApoA1/ApoB ratio relative to baseline; increased TAC and SOD compared to baseline; reduced lipid peroxidation biomarkers (MDA and ISP) compared to baseline. |

5. ACTIONS OF ASTAXANTHIN

1. Improves Brain Health

As you get older, the risk of developing neurodegenerative disorders like Alzheimer's or Parkinson's disease continues to increase. These conditions, which are characterised by the progressive loss of neurons in the brain, can lead to symptoms like memory loss, confusion, tremors, agitation and anxiety.

A good amount of emerging research has found that astaxanthin benefits brain health by preserving cognitive function. Year- 2016 animal study, for example, supplementation with astaxanthin increased the formation of new brain cells and enhanced spatial memory in mice. A review published in *GeroScience* also noted that the neuroprotective properties of astaxanthin may be due to its ability to reduce oxidative stress and inflammation. Coconut oil, avocados, walnuts and beets are just a few examples of other brain foods that boost focus and memory.

2. Protects Your Heart

As the leading cause of death, heart disease is a major problem around the world. While there are many potential causes of heart disease, oxidative stress and inflammation are believed to be front and centre more often than not.

According to a review out of Australia, there have been at least eight clinical studies measuring the effects of astaxanthin that have shown that astaxanthin supplementation may lower markers of both inflammation and oxidative stress. Another review published in the journal *Marine Drugs* suggested that astaxanthin could protect against atherosclerosis, the buildup of fat and cholesterol in the arteries. Of course, a healthy diet containing astaxanthin is just one piece of the puzzle. Minimising your stress levels, getting in plenty of physical activity and cutting out ultra-processed foods are also key factors to keep your heart in tip-top shape.

3. Helps Skin Health

In addition to boosting brain and heart health, astaxanthin benefits skin health as well. Studies show that it can both improve the overall appearance of skin and may also be able to treat certain skin conditions. Studies showed that combining oral supplementation and topical application of astaxanthin improved wrinkles, age spots, skin texture and moisture content of the skin.

Similarly, an animal study published in *PLoS One* also found that astaxanthin was able to significantly improve symptoms of atopic dermatitis in mice. In addition, astaxanthin protects "against UV-induced skin deterioration and helps maintain healthy skin in healthy people," according to a randomised, double-blind, placebo-controlled trial in healthy study participants. For best results, use astaxanthin in combination with a natural skincare routine, including other ingredients like tea tree oil, apple cider vinegar and shea butter.

4. Eases Inflammation and Improves Immunity

Inflammation is an important part of the body's immune response. Chronic inflammation, on the other hand, can contribute to conditions like diabetes, cancer and heart disease. Many studies have found that astaxanthin can reduce markers of inflammation in the body.

This could have far-reaching benefits and may even reduce the risk of certain types of chronic disease. In fact, a review out of China even reported that astaxanthin could have anticancer effects and may help prevent the proliferation and spread of cancer cells. However, further research in humans is needed to understand how astaxanthin may affect inflammation and disease in humans.

Not only does this antioxidant help to temper all-body inflammation, it also helps to enhance immunity. Year-2010 randomised, controlled trial found that supplementation with astaxanthin increased the immune response of subjects as it also reduced oxidative stress, including one specific marker of DNA damage that could potentially translate to disease later in life.

Other high-antioxidant foods that can help relieve inflammation and ward off disease include turmeric, ginger, dark chocolate and blueberries.

5. Enhances Your Workout

Whether you're looking to kick up your workout routine or give your energy levels a boost at the gym, an extra dose of astaxanthin may be able to help. Studies show that it may have multiple beneficial effects when it comes to upping exercise performance and preventing injury.

One animal study published in the journal *Biological & Pharmaceutical Bulletin*, for instance, found that astaxanthin supplementation improved swimming endurance in mice. A study in 2011 published in the *International Journal of Sports Medicine* also found that astaxanthin improved cycling time trial performance among 21 competitive cyclists. Meanwhile, another animal study in Japan showed that astaxanthin was even able to help prevent exercise-induced muscle damage in mice.

Want to boost your workout even more? Check out these post-workout meals that can help supply your body with the nutrients it needs after hitting the gym.

6. Boosts Male Fertility

It's estimated that infertility affects about 15 percent of couples worldwide, with male infertility contributing to up to 50 per cent of cases. Hormonal imbalances, problems with ejaculation and varicocele, or the swelling of the veins in the scrotum, are all common causes of male infertility.

Promising research has found that astaxanthin benefits male fertility and may help improve sperm quality. A small study conducted at Ghent University Hospital actually found that astaxanthin improved the movement of sperm cells and enhanced the ability of sperm to fertilise eggs. Additionally, men treated with astaxanthin achieved higher rates of pregnancy compared with a placebo group.

7. Supports Healthy Vision

Eye problems like macular degeneration and cataracts are common concerns associated with ageing. These conditions can cause a wide array of symptoms, ranging from blurry vision to complete vision loss.

So, what does astaxanthin do for your eyes? Fortunately, several studies have found that astaxanthin can improve the health of the eyes and help maintain 20/20 vision.

A 2008 animal study showed that astaxanthin helped protect retinal cells against oxidative damage. Another study comprising 48 adults complaining of eye strain found that a supplement containing several nutrients, including astaxanthin, helped reduce symptoms of eye fatigue.

8. Improves Cognitive Function

Many antioxidants have a reputation for improving cognition, which isn't that surprising. After all, reducing oxidative stress allows many parts of the body to function more efficiently. Astaxanthin is no exception — a randomised, controlled trial published in 2012, involving 96 subjects, reported a significant improvement in cognition after being supplemented with the antioxidant for 12 weeks.

Dosage

If you're getting it from whole food sources, you should try incorporating a few servings of astaxanthin-rich foods into your diet per week. These foods are especially beneficial because most provide an array of important nutrients in addition to astaxanthin, such as vitamins, minerals and omega-3 fatty acids.

In supplement form, it has been studied and proven safe in doses of 4 to 40 milligrams daily for 12 weeks. However, the recommended dosage is four to eight milligrams, one to three times per day with your meals. Initially, it's best to start with a low dose and work your way up to assess your tolerance

6. SIDE EFFECTS

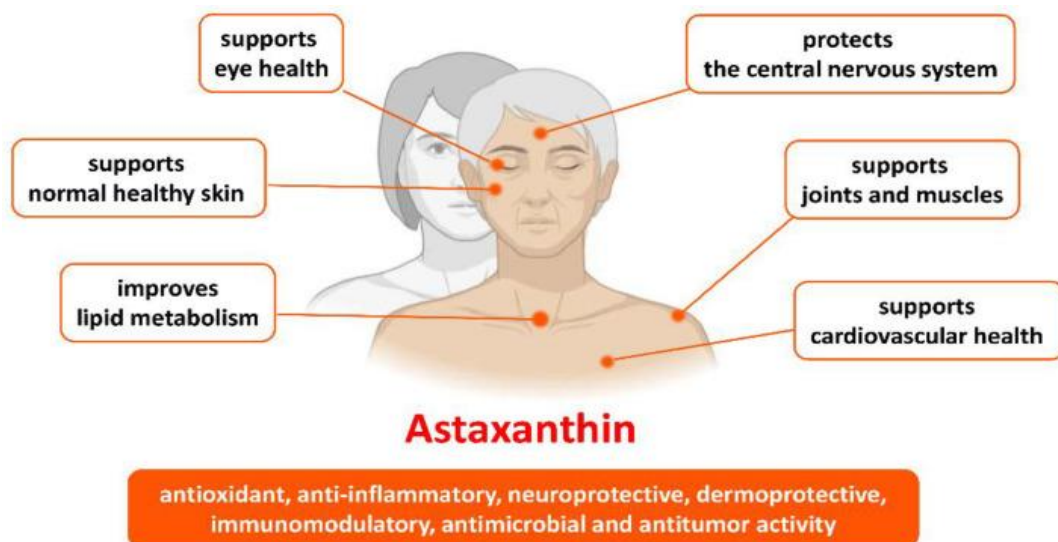
Astaxanthin is **Possibly Safe** when taken by mouth as a supplement. Astaxanthin has been used safely by itself in doses of 4 to 40 mg daily for up to 12 weeks. It has been used safely in combination with other carotenoids, vitamins, and minerals at 4 mg daily for up to 12 months. Side effects of astaxanthin may include increased bowel movements and red stool colour. High doses of astaxanthin may cause stomach pain.

7. SPECIAL PRECAUTIONS & WARNINGS

Pregnancy and breast-feeding: Not enough is known about the use of astaxanthin during pregnancy and breastfeeding. Stay on the safe side and avoid use.

Recommended Intake Dosage:

- 0 to 6 months: 4 milligrams (mg) or 6 IU per day
- 7-12 months: 5 mg or 7.5 IU per day
- 1-3 years: 6 mg or 9 IU per day
- 4-8 years: 7 mg or 10.4 IU per day
- 9-13 years: 11 mg or 16.4 IU per day
- 14 and up 15 mg or 22.4 IU per day
- Breastfeeding women: 19 mg or 28.4 IU per day



8. CONCLUSION

Astaxanthin is a xanthophyll reddish-orange carotenoid that shows significant biomedical applications. It is synthesised naturally by different living organisms, such as microalgae, fungi, lichens, and bacteria; it can also be produced biotechnologically. Besides, the reddish flesh of some animals (salmon, shrimps, lobsters, crayfish, etc.) is due to feeding on the Astaxanthin-producing organisms. Oxidative stress is a key contributor to several diseases, including ageing and age-related disease. The significant antioxidant, anti-inflammatory, neuroprotective, skin-protective, immunomodulator, antimicrobial, and anticancer activity, as well as the ability to improve lipid metabolism, make Astaxanthin a promising compound for the prevention or even treatment of different health conditions. An additional important role of Astaxanthin has been reported, i.e., suppressing the development of lifestyle-related diseases, such as diabetes. Strong evidence shows that Astaxanthin holds great promise for those wishing to prevent cognitive diseases and maintain general brain health. The implications of the studies cited above are extremely exciting, as the proportion of the elderly and the number of patients with cognitive decline increase in the population. Researchers validated the significant benefits of Astaxanthin supplementation for healthy ageing. Consequently, the demand and research for natural Astaxanthin for human health are increasing extensively worldwide. This review highlighted important Astaxanthin-associated clinical trials and explored many clues for research on the nutritional aspects of healthy ASX to learn much more about its value for healthy ageing and for the management of age-related disorders.

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