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The effects of antioxidants on various body systems and physical activity - a literature review on Astaxanthin

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Abstract: Astaxanthin is an organic fat-soluble compound from the xanthophyll group derived mainly from marine organisms. It has greater antioxidant properties than vitamins e, c and beta-carotene. It may have potential applications in various areas of medicine and dietetics. The safe daily dose appears to be 6-8 mg per day. Its use may be beneficial in cardiology by lowering insulin resistance, improving lipid profile and reducing the extent of myocardial infarction. In addition, it improves cognitive function and has beneficial effects on skin properties such as texture and hydration. Its positive effects on visual acuity have also been proven. Its use can increase fat burning during aerobic exercise and increase physical performance during exercise. Considering the available research results, astaxanthin seems to be a promising supplement with strong antioxidant properties. Most of the studies, however, were conducted on animals and more human studies are needed. The purpose of this work is to summarize the available knowledge regarding this unique substance. The article reviews studies and scientific papers available in PubMed databases on Astaxanthin for the period 2010-2023.

Keywords: Astaxanthin, supplements, health, antioxidant

Introduction: Astaxanthin is an organic chemical compound from the group of xanthophylls. It is a metabolite of zeaxanthin and cataxanthin. Similar to many other carotenoids, it is fat-soluble. The astaxanthin molecule has numerous conjugated multiple bonds, which determine the color of the substance and its antioxidant properties (1). Astaxanthin (ATX) , which belongs to the group of natural carotenoids, has very strong antioxidant properties. For example, compared to:

- vitamin E it is 14 times more potent

- vitamin C it is 65 times more potent

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- ß-carotene it is 54 times more potent (2).

It is mainly found in marine ecosystems, especially in aquatic animals such as shrimp, salmon, trout, crayfish, krill, etc. It is also being synthesized by microalgae such as Heamatococcus pluvialis (3,4).

Buser, Jovanovic, Lenz et al. conducted a study on rats, based on which, in 2014, the Panel on Feed Additives and Products or Substances Used in Animal Feed (FEEDAP) established the tolerable daily intake of synthetic ATX in foodstuffs at 2 mg/day for a 60-kg adult (5).

In the European Union, a new food regulation entered into force in 2018 confirming a maximum safe level for ATX of up to 8 mg. The Food and Drug Administration [FDA] suggests the safety of astaxanthin sourced from H. pluvialis, provided consumption does not exceed 6-7 mg per day (6).

No significant adverse reactions were reported at the recommended doses. In a test in which participants took doses of 30 mg, a red coloration of the stool was observed (7). This was also demonstrated in a study using 20 mg of astaxanthin, in which increased bowel movements were additionally noted (8). Natural astaxanthin is being sold in the European Union in a variety of products in daily doses of up to 12 mg and has been authorized by relevant national authorities throughout the world in daily doses of up to 24 mg. There have been at least 87 clinical studies involving more than 2,000 participants using short-term daily doses (up to 100 mg) and long-term daily doses of an average of 8 to 12 mg. No evidence of significant toxicity was observed at any dose for any duration in a given period (6).

Materials and methods

The article reviews studies and scientific papers available in PubMed databases on Astaxanthin for the period 2010-2023.

Results and discussion:

1. Cardiovascular system:

The progression of atherosclerotic cardiovascular disease is associated with the effects of inflammation and oxidative stress on the organism. Therefore, an agent with strong antioxidant and pre-inflammatory effects was searched for to counteract the pathophysiological cardiovascular processes. Astaxanthin appears to be one such product. It extinguishes singlet oxygen more effectively than other antioxidants for example beta-carotene and lutein (9), and in addition, its polarity enables it to be positioned strategically in cell membranes (10).

Dietary supplements and antioxidants mitigate the progress of atherosclerosis and reduce protein and lipid oxidation (11,12). Conversely, lower dietary consumption of antioxidants is related to the occurrence of inflammation and oxidative stress (13).

Regrettably, the majority of research using antioxidants such as vitamin E, vitamin C and beta-carotene as agents to avoid cardiovascular incidents or reduce mortality has not shown satisfactory results. It has not been clarified whether this was due to the use of readily available, low-cost agents in most of the studies, or to their use over

too short a period of time, or to the selection of patients to the study group at a stage of the disease that was too advanced (14,15,16). Further studies evaluating more powerful antioxidants such as astaxanthin should be pursued in the future. In particular, in patients with evidence of the presence of oxidative stress.

In 2010, in a study in mice, astaxanthin showed positive effects on thrombosis (17). In other trials, it also revealed a decrease in inflammation (18,19) and reduced lipid peroxidation [20]. Li, Hellsten, Jacobsson et al. conducted a study in rabbits that showed astaxanthin enhanced atherosclerotic plaque stability and reduced macrophage infiltration in the plaque (21). An improvement in insulin sensitivity in rats, as well as a lowering of blood pressure was observed after astaxanthin use (22). Studies in gestational diabetic mice have shown that astaxanthin, by promoting GLUT4 translocation to the plasmatic membrane, increases sensitivity to insulin. In addition, astaxanthin was also detected to markedly increase glucose consumption by muscles (56).

Animal studies showed a notable reduction in myocardial infarct size when astaxanthin was administered for 4/5 days at a dose of 50 mg/kg body weight per day. There was even a reported case of two out of three dogs in which the use of intravenous supplementation resulted in full protection of the heart muscle from myocardial infarction (23,24). Astaxanthin may ameliorate some of the detrimental effects of diabetes through an endothelial-dependent improvement of relaxation in aortic rings. Animal studies have also shown promising effects of astaxanthin on improving lipid profile . The most significant impact appears to be on reducing plasma triglyceride concentrations. In addition, an effect on white adipose tissue was observed by reducing the fat cell size (25).

A trial of 27 Korean men with a BMI above 25 who had been supplemented with 20 milligrams of astaxanthin daily for 12 weeks showed a remarkable decrease in ApoB by 7.59% and LDL by 10.4% (26).

A study conducted in 2020 showed that astaxanthin, by improving the antioxidant enzyme activity, was also involved in the rebuilding of vascular smooth muscle cells and thus diminished their proliferation and oxidative stress-induced damage (27).

As a powerful antioxidant, astaxanthin lowers the concentration of oxygen free radicals, which are in charge of LDL oxidation and peroxidation of lipids. Since it can accumulate in plasma, it influences vasodilation and has an anticoagulant effect by raising the activity of antioxidant enzymes. It also has a beneficial effect on erythrocytes by preventing loss of their elasticity and counteracting elevated blood viscosity. All of this contributes to prevention of the early stages of formation of coronary plaques and thus postpones the development of cardiovascular disease (28).

2. Nervous system:

Neuroinflammation, oxidative stress and excitotoxicity, as neurotoxic agents affect the induction of brain cell death. Latest findings have given carotenoids a prominent position in the therapy of neurodegenerative diseases. Carotenoids extracted from marine algae alleviate neuroinflammation by inhibiting COX-2 and iNOS expression, modifying MAPK and the inactivation of NF-κB (29).

Studies in rats have shown that astaxanthin can cross the blood-brain barrier easily, protecting the brain from both chronic neurodegeneration and acute damage. One study showing a mouse ischemic stroke model showed that astaxanthin pretreatment reduced oxygen radical production and mitigated lipid peroxidation and additionally reduced brain infarcts (30,31). Astaxanthin has been shown to be accumulated in the cerebral cortex and hippocampus of rat brains after both single and repeated intake. It has been suggested that astaxanthin accumulation in the cerebral cortex may influence the maintenance and enhancement of cognitive function (32).

The following study results stand out:

-increase in processing speed and psychomotor speed (33).

-Improvement of complex memory and verbal memory (34).

-Decreasing the area of infarction and increasing the vitality of nerve cells (35).

Two placebo-controlled trials have revealed that oral intake of astaxanthin can successfully upgrade cognitive abilities, helping patients with Alzheimer's disease perform tasks faster and more accurately (33,34).

A different research has shown that astaxanthin has protective properties against some nerve cells. The protection relates to neurotoxicity stimulated by cytotoxicity induced by glutamate and decreased release of lactate dehydrogenase (36).

A 2019 study found that astaxanthin alleviates inflammation by lowering levels of TNF-a, IL-1b and IL-6 measured at 6 and 24 hours after SAH and affects higher survival of neurons after subarachnoid hemorrhage. The effect of astaxanthin as a potential agent with a wide therapeutic window in the treatment of subarachnoid hemorrhage was also evaluated. The results turned out to be very promising, as they revealed that treatment with ATX within 30 minutes or 4 hours after SAH markedly alleviated apoptosis of neurons, enhanced behavioral functions and lowered neurological deficits, while application of the drug after 8 hours no longer showed such properties. (37).

The neuroprotective effect is also explained by its contribution to stabilizing the mitochondrial membrane potential, as well as by modifying the Akt/Bad and Nrf2-ARE pathways and the toll-like receptor signaling pathway 4 (38,39). In conclusion, protective impact on the nervous system is a promising activity of astaxanthin.

3. Skin:

Astaxanthin has singlet oxygen radical scavenging properties in the dermis and epidermis which can lead to improved elasticity of the skin and reduced depth of wrinkles. It also has regulatory capacities against endogenous antioxidant enzymes such as superoxide dismutase 2 (SOD 2), catalase (CAT) and glutathione peroxidase 1 (GPX1). This reduces the activation of oxygen radical-producing enzymes and xanthine oxidase in UV-irradiated cells (40).

One of the conducted clinical trials examining the effects of astaxanthin supplementation on skin health was an open-label, prospective study in 2017 in which 31 people over the age of 40 took astaxanthin at a dose of 4mg

per day for 4 weeks. Inverted signs of skin changes were observed in regard to corneocyte exfoliation, the presence of microorganisms and the size of lipid droplets, in particular in obese people (41).

Ito et al conducted a randomized, double-blind study among healthy subjects aged 30-56 years that lasted 10 weeks and included dosage of astaxanthin supplementation at 4 mg per day. Attendees have reported subjective skin texture and appearance improvements. In addition, it has been found that astaxanthin prevents UV radiation and lowers skin hydration loss (42).

Other studies have shown the following results (43):

-Enhanced cellular and humoral immune response with a higher total subpopulation of T and B lymphocytes

- Reduced plasma concentrations of 8-OHdG (a biomarker of DNA damage) and C-reactive protein

-Enhanced elasticity and integrity of the epidermis

-Diminished skin redness

- Reduced visually noticeable wrinkles and age spots

A study by Yoshihisa et al. showed that astaxanthin, by reducing the production of the inflammatory factors such as IL-1β and TNF-α and oxidative factors such as inducible nitric oxide, is able to defend keratinocytes against ultraviolet radiation damage (44).

4. Eye Health:

Astaxanthin exerts its effects on the eyes by raising blood flow in the retinal capillaries in the area of the optic nerve disc. It has the potential to repair ciliary body function through improved circulation of blood. Thus, it can lead to a reduction in eye tiredness and an improvement in accommodative function, as well as reduce shoulder tension (45).

Astaxanthin restores the balance between pro-oxidant and antioxidant factors and effectively prevents the formation of ROS. It is hoped to stop the onset and also the progression of diseases associated with a pro-oxidant environment (46,47). Studies in rats have shown that astaxanthin greatly decreases apoptosis of retinal ganglion cells, which is in charge of the advancement of the retina damage in glaucoma and other neuropathies of the optic nerve (48). Parisi and co-authors carried out a comparative trial in humans to examine the effect of oral supplementation with carotenoids, among them astaxanthin, on retinal functioning in AMD. The study involved 27 patients with non-advanced AMD who were divided at random into two groups: 15 patients received oral supplementation of astaxanthin 4 mg daily and a combination of other antioxidants for 12 months, while the remaining 12 patients received no treatment at all. Patients who took the supplements demonstrated better central retinal function compared to the placebo group. Improvements in the pattern of the electroretinogram were also noted (49). Piermarochi et al. conducted a randomized prospective study in which patients with AMD were treated with zeaxanthin, lutein and astaxanthin for 2 years. After the treatment period, patients reported improved contrast sensitivity, improved visual acuity and overall better visual functions (50).

5. Exercise supplement:

During animal testing, astaxanthin showed beneficial effects on physical activity, including (51) :

- Extended time to exhaustion by enhancing lipid metabolism.

- Elevated levels of PGC-1alpha in skeletal muscle.

- Amplified biogenesis of mitochondria through the AMPK pathway

- Decreased skeletal muscle atrophy via redox balance

- Spatial memory enhancement with increase in hippocampal neurogenesis

- Decreased rate of atrophy of unused muscles by suppressing oxidative stress.

Whereas in one of the studies astaxanthin inhibited activity-induced Nrf2 production and induction of intra-secretory antioxidant enzymes at increased levels of doses (52).

During a study on rats, researchers showed muscle glycogen depletion and an increase in the rate of fat oxidation throughout physical activity. This may imply an ergogenic astaxanthin mechanism of action (53). A study published in February 2023 describes 19 overweight patients who were enlisted and given 12 mg of astaxanthin or placebo supplementation for 1 month. Patients finished a graded cycling ergometer exercise test to investigate variations in the rate of substrate oxidation. A remarkable reduction in CHO oxidation was observed from the period before to the period after supplementation alone in the astaxanthin group. Moreover, the astaxanthin group showed a 7% decline in heart rate in the graded effort test. Taken together, these results imply that 4-week supplementation might also offer certain cardiometabolic advantages to people who are overweight and be a beneficial addition for those starting an exercising (54).

On the whole, experiments in rodents suggest improved endurance performance with astaxanthin, albeit with potential impairment of certain skeletal muscle workout adaptations. Considering these results and the absence of studies in humans, future investigations need to concentrate on the impact of astaxanthin on endurance capacity and training-related adaptations in human skeletal muscle (55).

Conclusions:

The use of astaxanthin on animals has found positive effects on cardiovascular and nervous system function. It was observed to improve the quality of vision, benefit the condition of the skin and improve the physical performance of the body during exercise. However, it should be noted that most of the studies were conducted on animals. It may be beneficial to carry out more studies on humans. Perhaps this compound could prove to be an effective supplement used in various medical fields.

Author Contribution Statement:

Conceptualization, Natalia Kusak, methodology- Gracjan Rudziński; software- Aldona Pażyra; check- Natalia Żak ; formal analysis- Barbara Jaworska; investigation- Paweł Stanicki; resources- Natalia Kusak; data curation- Gracjan Rudziński; writing - rough preparation- Natalia Kusak; writing - review and editing- Aldona Pażyra; visualization- Barbara Jaworska; supervision- Natalia Żak; project administration- Paweł Stanicki; receiving funding-.

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