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Effect of Astaxanthin on Exercise Ability

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Abstract

High-intensity exercise will induce the production of reactive oxygen species. If a large amount of it accumulates in the body, it will cause oxidative stress, cause cell oxidative damage, break the redox balance, and affect your own health. The human body has its own oxidative damage protection system, that is, when the oxidative balance in the body is broken, it will produce non-enzymatic antioxidants such as vitamin E, vitamin C, carotenoids, etc. to protect the body from oxidative damage. With the emergence of various supplements, reducing the active oxygen and reactive nitrogen (ROS/RNS) produced by exercise through exogenous intake of antioxidants has become a popular antioxidant model. As a powerful antioxidant, astaxanthin has gradually become a hot topic. In addition to its antioxidant capacity, it also has the ability to relieve fatigue, promote recovery, and anti-inflammatory. This article mainly discusses the role of astaxanthin as an antioxidant from the perspective of exercise. The performance mechanism in the body is intended to provide a reference for reducing the oxidative damage of the human body during exercise.

Keywords

Astaxanthin; oxidative stress; exercise; antioxidant.

1. Introduction

Scientific exercise will promote human health, but if the exercise becomes too intense, the body will produce excessive ROS and overwhelm the endogenous antioxidant defense system, resulting in oxidative stress, and lipid, protein and nucleic acid molecules will be damaged, which will have an adverse impact on normal physiological functions [1]. At present, studies have proved that antioxidants can prevent and delay cell oxidative damage by removing, inactivating and preventing the formation of ROS, and can significantly delay or prevent the oxidative damage of target molecules [2]. Therefore, more and more antioxidants and antioxidant products appear and are used in competitive sports, entertainment sports and other aspects. At present, various antioxidants on the market are constantly updating, so the emergence of antioxidants is more worthy of our research. The recent emergence of astaxanthin, the "king of popular antioxidants", has brought the theory of antioxidants eliminating free radicals to a higher level. Astaxanthin is a natural antioxidant. In terms of antioxidant activity, astaxanthin is 10 times higher than other carotenoids, such as zeaxanthin, lutein, carotene and keratin. In recent years, astaxanthin has been studied in the field of sports. Many studies show that astaxanthin can reduce the oxidative damage of skeletal muscle and myocardium related to sports [3], promote lipid metabolism during sports [4] and improve endurance performance. In addition, it is reported that astaxanthin also has anti-inflammatory effects [5,6], indicating that its remarkable biological activity makes it have broad development prospects.

2. Bioactivity of astaxanthin

The chemical name of astaxanthin is 3,3 '- dihydroxy-4,4' - diketone- β，β'- Carotene, with the molecular formula $C_{40}H_{52}O_4$, belongs to terpene unsaturated compounds. Astaxanthin is similar to

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other carotenoids in structure and has a conjugated double bond long chain structure, but there are carbonyl and hydroxyl groups at both ends of the conjugated double bond chain α- Hydroxyketone structure and this conjugated structure have active electronic effect, which significantly enhances the electronic effect of astaxanthin. Therefore, astaxanthin has a good ability to scavenge oxygen free radicals [7].

Astaxanthin exists in three different forms, which are associated with two hydroxyl groups: 1) the non-esterified form in which both hydroxyl groups are unmodified; 2) the monoesterified form in which one hydroxyl group is esterified with fatty acids; and 3) the bis-esterification form in which both hydroxyl groups are unmodified. It is currently believed that astaxanthin extracted from red algae is mainly the monoesterified form, while astaxanthin from Fife yeast is almost always the non-esterified form. Aoi et al [8] found that mice fed the esterified astaxanthin group, which exercised for the longest time until exhaustion, had significantly higher plasma and tissue concentrations of astaxanthin than the other groups, which is thought to be due to the fact that esterified astaxanthin, due to its good absorption properties, better promotes energy production during exercise The esterified form of astaxanthin has a higher antioxidant activity and better effect than the non-esterified form of astaxanthin due to its good absorption properties and protection of tissues from oxidative damage.

3. Antioxidant capacity of astaxanthin

In 2016 Janina [9] demonstrated by electron spin resonance (ESR) technique and spin trapping and photon counting oxygen burst activity that astaxanthin exhibits important free radical scavenging, oxygen burst and antioxidant activities in addition to its coloring properties. Later, VISIOLI et al [10] found that astaxanthin quenches single-linear oxygen scavenging radicals by forming resonance-stabilized carbon centers through a polyolefin chain with electronically conjugated double bonds. As the number of conjugated double bonds of astaxanthin increases, its ability to quench reactive oxygen species is enhanced [11]. The common chemical feature of carotenoids is the polyene chain, a long conjugated double bond system that terminates the antioxidant activity of carotenoids by quenching singlet oxygen and scavenging free radicals to terminate the chain reaction [12], and the structural similarity of astaxanthin to other carotenoids makes the remarkable antioxidant activity the most important physiological function of astaxanthin. The ability to scavenge hydroxyl radicals and quench singlet oxygen is an important test of the antioxidant properties of natural substances, and in studies on the mechanism of astaxanthin antioxidant activity since the powerful antioxidant properties of carotenoids may be related to specific physicochemical interactions of membranes, McNulty [12] et al. evaluated the effects of astaxanthin, zeaxanthin, lutein, b-carotene, and lycopene on the antioxidant activity of membranes rich in polyunsaturated fatty acid-rich membranes, found that non-polar carotenoids, such as lycopene and b-carotene, disrupt membrane bilayers and have potent pro-oxidant effects, when lipid hydrogen peroxide levels increase by 85%, whereas astaxanthin protects membrane structure, with significant antioxidant activity and a 40% reduction in lipid hydrogen peroxide levels, suggesting that carotenoids, due to membrane structure altered membrane structure and had a significant effect on lipid peroxidation. Carotenoids have different chemical antioxidant and pro-oxidant effects due to the different structure of the terminal groups, the number and position of the methyl groups, and through experiments Goto [13] et al. showed that astaxanthin captures free radicals not only in the conjugated polyene chain but also in the terminal ring portion, where the C3-methyl hydrogen atom of the terminal ring is a free radical capture site. In order to investigate the biochemical effects associated with astaxanthin in the organism, researchers have started to use various experimental methods to explore them. Rufer et al. used a high performance liquid chromatography method of analysis [14], an experiment in which 28 healthy men were selected for a 4-week investigation and found that in the case of long-term astaxanthin intake, maximum concentrations could be reached and maintained within the first week of ingestion, even if astaxanthin was obtained from different sources. Also Brown [15], in a plasma study of elimination kinetics, found that maximum concentrations could be reached and at steady state within 7 days of the amount

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of astaxanthin ingested by the organism. Therefore, it can be concluded that regardless of the source, state and manner of astaxanthin ingestion, its bioavailability can be optimized within 7 days after elimination of the relevant kinetics.

Astaxanthin intake has a very good safety profile. Clinical studies have shown that after a 4-week intervention in humans at higher doses of astaxanthin (ingested in rainfed sea bacterium, 40 mg per day) did not show any harmful effects [16]. In terms of absorption, astaxanthin is absorbed by fat molecules and then delivered directly to target organs or tissues, such as the brain, retina, and skeletal muscle, due to its simultaneous lipophilic and hydrophilic nature [17]. Therefore, it is recommended to consume astaxanthin along with fat for more than 7 consecutive days to ensure optimal intake. Thus, it seems that astaxanthin has considerable potential and promise for human health and nutrition [18].

Researchers are beginning to use animal studies to demonstrate that astaxanthin is also an unsurpassed antioxidant for the biological circulatory system. Initially, in an animal study in 1991, researchers found that the concentration of catalase (CAT) and superoxide dismutase (SOD) in plasma and hepatocytes of rats fed with rainfed red algae powder increased significantly. Subsequently, researchers began to pay hot attention and conduct deeper related experiments on them, and until recent years there are still relevant reports, such as rats induced with Aβ25-35, the biochemical indexes malondialdehyde (MDA) and SOD activity increased and lactate dehydrogenase (LDH) activity decreased after using astaxanthin, suggesting that astaxanthin has extremely strong antioxidant properties and can promote the production of reactive oxygen radicals, etc. [19]. Wu et al[20] found that astaxanthin prevented the opening of the mitochondrial permeability transition pore in neuroblastoma by inhibiting the production of constitutive ROS and reducing ROS levels (especially in mitochondria). Subsequently, related experiments confirmed [21] that astaxanthin could inhibit lipid peroxide formation by inhibiting the production of reactive oxygen species and enhance the antioxidant enzyme status of glycated protein/iron chelator-exposed endothelial cells.

From a research perspective, our focus is often not limited to normal physiological states and even in the clinical context more and more physiological injuries are becoming focused on this amazing antioxidant, and there is growing evidence that astaxanthin can reduce oxidative stress. Ischemia-reperfusion injury is currently considered to be an important cause of increased oxygen radicals, researchers have established a mouse model of renal ischemia-reperfusion as well as liver ischemia-reperfusion and treated with astaxanthin interference, both of these 2 studies suggest that pretreatment of test animals by astaxanthin intervention can significantly increase serum SOD levels and accelerate the scavenging of oxygen radicals, and the antioxidant activity of astaxanthin is important for maintenance of renal and hepatic functions and histological structures after ischemia-reperfusion with significant protective and reparative effects [22,23].

Oxidative stress is a major factor in the pathogenesis of various human diseases and the aging process. Mitochondria are the center of cellular metabolism and are the main regulators of redox homeostasis, exerting antioxidant effects, and are key to cell development and progression. Increased oxidative stress damages mitochondria and subsequently mitochondrial dysfunction, leading to an excess of mitochondrial reactive oxygen species, which causes cellular damage. It was found [26] that astaxanthin is an important factor in maintaining membrane potential ($\Delta\Psi$), high respiratory rate and mitochondrial redox state when exposed to oxidative conditions, even at nanomolar concentrations, when under oxidative stress, when astaxanthin not only maintains high mitochondrial membrane potential and respiratory stimulation, but also improves mitochondrial function and redox state, and the free state of astaxanthin. Astaxanthin can eliminate free radicals by reacting with them and improve the antioxidant capacity of the body. Clinicopathological studies have found that astaxanthin can prevent mitochondrial apoptosis by inhibiting the release of cytochrome C in whole-body irradiation injury [27] and burn inflammation models [28,29]. Astaxanthin has now been shown to be one of the most effective antioxidants against lipid peroxidation and oxidative stress in both in vivo and ex vivo environments [30,31]. Astaxanthin supplementation inhibits the accumulation of

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damaging reactive oxygen species in mitochondrial membranes [32] and also upregulates the expression of adenylate-activated protein kinase (AMPK) α-1, peroxisome proliferator-activated receptor (PPAR)-γ in skeletal muscle mitochondria, promoting mitochondrial biosynthesis [33] and maintaining mitochondrial function, astaxanthin has been suggested to protect lipid-rich during oxidative stress by broadly structures from peroxidation, and such studies should also be progressively used to study oxidative stress caused by acute exercise or and exercise in hypoxic conditions.

4. Effect of astaxanthin against exercise fatigue

4.1 Astaxanthin and exercise capacity

Since the 19th century, a large number of studies have attempted to explain the mechanism of sports fatigue from different perspectives, and several hypotheses have been developed independently, among which the more important ones are the "depletion theory", "blockage theory", "internal environment although various tests and experiments have shown that astaxanthin's natural antioxidant function is currently the most ideal antioxidant, in the field of sports science, astaxanthin has also been proven to have the ability to reduce exercise fatigue, increase muscle strength and muscle endurance, and reduce the intra-muscular inflammatory response caused by strenuous exercise. The effects of astaxanthin on intramuscular inflammatory responses caused by strenuous exercise [34]. In 2003 [3] researchers investigated the effects of astaxanthin dietary supplementation on delayed injury in mice after strenuous exercise and found that muscle glycogen concentrations were significantly higher in the astaxanthin group compared to the control group, suggesting a potential glycogen retention effect that could alleviate the fatigue and increase muscle endurance, while confirming that astaxanthin accelerates fatigue recovery by directly scavenging reactive oxygen species and downregulating the inflammatory response. In a recent human trial [35], astaxanthin was found to improve muscle strength and endurance in older adults when taken for 4 months (12 mg/d) in combination with functional training.

4.2 Mechanism of "depletion theory" of astaxanthin on fatigue

According to the "depletion theory" of fatigue, in order to confirm the ability of astaxanthin to fight and recover from fatigue, researchers believe that since fat is a source of energy, its metabolic pathway is from long-chain fatty acids into the mitochondria, a process that requires the mitochondrial carnitine palmitoyltransferase (CPT) complex, especially CPT1 regulatory enzymes. enzymes. Because of its lipophilic properties, astaxanthin accumulates on the mitochondrial membrane after ingestion and provides protection against damage caused to its function [26], therefore, astaxanthin could protect CPT1 and thus indirectly enhance fat metabolism during exercise [4], allowing it to provide energy during exercise and reduce the time for fatigue to appear. During exercise, elevated levels of NEFA in the blood are due to the enhanced role of lipid metabolism in the body to maintain the energy supply for muscle contraction. Increased fatty acid utilization during exercise reduces the rate of glycogen consumption and improves endurance exercise performance [36-38], therefore, fatty acid utilization is considered to be an important factor influencing endurance exercise. Thus Aoi et al [4] investigated this hypothesis using an exercise mouse model, where 4 weeks of astaxanthin supplementation resulted in significantly higher muscle glycogen concentrations and tended to have higher plasma non-esterified fatty acid (NEFA) concentrations in the astaxanthin group compared to the control group, and also 21% higher fat oxidation and 12% lower carbohydrate oxidation in another group of mice using the same supplementation regimen compared to the control group. Recent experimental studies in humans are now available [39], showing that athletes who underwent even only 7 days of astaxanthin supplementation during endurance exercise had significantly higher rates of body fat oxidation than those with unsupplemented athletes, enhancing exercise tolerance and exercise-induced fatty acid metabolism [40].

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4.3 Mechanism of astaxanthin to improve the dysregulation of internal environmental homeostasis

After understanding the doctrine of dysregulation of internal environmental homeostasis, Mayumi [36] reported that gavage of astaxanthin in mice significantly reduced blood lactate concentration, decreased plasma free fatty acid and blood glucose depletion, prolonged swimming exhaustion time, improved locomotor performance, and increased the duration of exercise in rats in the cycle time experiment. In acute high-intensity exercise, the antioxidant capacity of the body is temporarily reduced, blood lactate level is sharply increased and blood uric acid level is slightly reduced, while the rise of blood lactate in the body after exercise can be significantly reduced and the clearance of lactate during the recovery period can be accelerated by astaxanthin supplementation [41]. Subsequently, researchers [42] used long-term astaxanthin supplementation with exercise in Wistar rats, whose is study showed significant relief of fatigue in the intervention group and found that this relief of fatigue was associated with redox homeostasis in the flounder muscle allowing it to improve exercise capacity, suggesting that intake of esterified astaxanthin may prevent oxidative damage to skeletal muscle mitochondria and also suggesting that it may inhibit The idea that lactate production and ultimately prolonged exercise time to fatigue was suggested. In addition, Miao Xiaobao et al [43] also found that astaxanthin infusion significantly increased the activity of NA^+-K^+ ATPase and $CA2^+$-$MG2^+$ATPase in rats or swimming rats under quiet death and immediately after exhaustive exercise, suggesting that astaxanthin infusion combined with exercise training can effectively inhibit the activity of NA^+-K^+ ATPase and $CA2^+$-$MG2^+$ATPase immediately after exhaustive exercise. The above experimental studies confirmed that astaxanthin is a good recovery agent for both acute and exhaustive exercise.

4.4 Mechanisms of Astaxanthin to Alleviate Inflammation

Exercise stress produces high levels of inflammatory factors that may contribute to the onset of fatigue and slow recovery from fatigue, and astaxanthin is thought to reduce inflammation and thus speed recovery from fatigue by inhibiting pro-oxidant factors and decreasing pro-inflammatory factors [3]. An in vitro study demonstrated [44] that after an intervention with 5-100 μM astaxanthin administration, the expression of pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β) was significantly inhibited compared to the control group.

Similar effects were reported through studies in an in vivo mouse model, where treatment with a 40 mg/kg^{-1} dose of astaxanthin also resulted in significant reductions in plasma NO, TNF-α and IL-1β. This experiment suggests a potential mechanism by which astaxanthin could promote recovery by inhibiting oxidative and inflammatory responses to physiological stressors, such as strenuous exercise. In support of this hypothesis, researchers used an exercise rat model [3] to supplement astaxanthin for 3 weeks after running at an intensity of 28 m/min^{-1}. Astaxanthin significantly reduced myeloperoxidase (MPO) activity in skeletal muscle tissue and cardiac muscle tissue and significantly downregulated plasma creatine kinase (CK) activity. Since MPO and CK are markers of secondary neutrophil infiltration and muscle damage, this also highlights the potential of astaxanthin to attenuate the inflammatory muscle damage response in the days following exertional exercise.

4.5 Antioxidant mechanism of astaxanthin

Harman proposed the free radical theory as early as 1956, proving that free radicals can exist independently in normal organisms and occur in a series of free radical damage reactions with a variety of biomolecules in the body, and that strenuous exercise increases the production of free radicals in the organism, while reactive oxygen species are the main cause of muscle redox homeostasis disorders, which leads to muscle fatigue and affects the exercise capacity of the organism. There have been many studies on enhancing antioxidant enzyme activity and promoting recovery from body fatigue through supplementation with exogenous antioxidants or antioxidant drugs, and astaxanthin is one of them [45]. During intense exercise training, a large number of relevant endogenous antioxidant compounds (i.e. superoxide dismutase, catalase, glutathione peroxidase) and non-endogenous antioxidant compounds (i.e. vitamin C, etc.) work in concert to ensure that the

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production of ROS does not become harmful [46]. The advent of astaxanthin has certainly allowed the field of exercise to find a novel antioxidant and anti-fatigue exercise supplement.

While antioxidant supplementation before, during and after exercise has long been a common "training additive", researchers have mimicked this supplementation by exogenously supplementing astaxanthin to demonstrate that even when exercise leads to an increase in reactive oxygen species that disrupt one's own antioxidant protection system, astaxanthin supplementation allows it to act as an antioxidant to reduce the damage caused by related factors caused by the damage. Through experiments Wang Chan [47] et al. found that rats trained in four weeks of incremental load endurance training and supplemented with natural astaxanthin reduced the production of skeletal muscle free radicals, scavenged free radical metabolites and reduced lipid peroxidation reactions compared to the control group. The myocardium is also an important part involved in the exercise process, and Wu Lijun et al [48] demonstrated that rats were pre-given a safe level of astaxanthin for 29 days, and after acute high-intensity exercise, it was found that the supplemented astaxanthin was effective in increasing plasma calcitonin gene-related peptide (CGRP) levels and inhibiting the elevation of myocardial endothelin (ET) in plasma and myocardial tissue, thus reducing myocardial lipid peroxidation and exercise injury, proving that astaxanthin can also reduce myocardial lipid oxidation, and the above studies are presented to prove that astaxanthin can reduce exercise injury and present a relevant reference for the field of exercise.

Nuclear factor erythroid 2-related factor 2 (Nrf2), indirectly regulates endogenous antioxidant defense lineages. During oxidative stress, modification of cysteine residues on Keap1 leads to the release and translocation of Nrf2 to the nucleus, where it binds to the antioxidant response element (ARE). Once activated, the Nrf2/ARE signaling pathway initiates the transcription of several cytoprotective genes as well as enzymes capable of upregulating the endogenous antioxidant response to oxidative stressors, potentially producing beneficial effects on exercise [49]. Studies have shown that astaxanthin can attenuate oxidative damage by interacting with a redox-sensitive transcription factor (Nrf2) [50-51]. Currently, the latest studies using nuclear magnetic resonance (1H-NMR) metabolomics techniques concluded that the increase in antioxidant capacity and exercise capacity of the organism during acute high-intensity exercise after astaxanthin supplementation is associated with changes in amino acid metabolism and lipid metabolism-related substances [31].

5. Conclusion

As the most significant and safe natural antioxidant in nature, astaxanthin has emerged as an excellent antioxidant not only in the field of sports, but also in reducing sports injuries and helping to relieve fatigue. The above studies have proved that astaxanthin has a very obvious effect as a dietary supplement for humans, and this review has made a strong proof for this argument, however, the negative or adverse experiments about astaxanthin are less reported, and we still need to explore its negative effects, so we need to continue to conduct relevant experiments in the future to further verify the physiological and biochemical effects of astaxanthin in all aspects Therefore, we need to continue to conduct experiments to further validate the physiological and biochemical effects of astaxanthin and to provide theoretical support for the further development of its beneficial potential in humans.

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