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Research Progress on Astaxanthin in Exercise-Induced Fatigue

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Abstract: Exercise-induced fatigue represents a complex physiological response triggered by physical exertion, with its mechanisms primarily originating from central and peripheral systems. Central fatigue arises from neurotransmitter imbalances such as elevated serotonin and reduced dopamine levels, leading to drowsiness and diminished motor performance. Peripheral fatigue occurs at the muscular level, where energy depletion, metabolic waste accumulation, and oxidative stress impair muscle contraction function. Astaxanthin, a potent antioxidant, directly and primarily alleviates peripheral fatigue through its antioxidant, anti-inflammatory, and mitochondrial protective effects. Simultaneously, by improving the peripheral environment and reducing the transmission of fatigue signals to the brain, it indirectly helps alleviate central fatigue. Based on this, this paper reviews the mechanisms of action and related research progress of astaxanthin on exercise-induced fatigue, and discusses its application value and challenges based on the current status.

Keywords: Exercise-induced fatigue; Astaxanthin; Mechanism of action; Oxidative stress; Anti-inflammatory

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1. Introduction

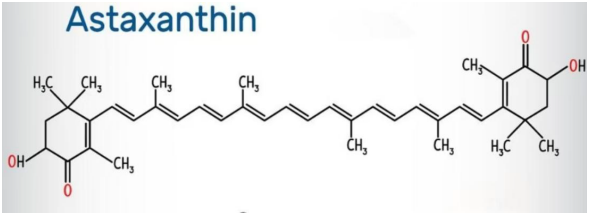
Astaxanthin (AST), specifically 3,3'-dihydroxy-4,4'-diketone-β, β'-carotene, is a multi-target liposoluble ketocarotenoid belonging to the xanthophyll family, which includes β-cryptoxanthin, β-carotene, lycopene, and zeaxanthin [1]. Derived from marine organisms, it was first discovered in lobsters and later identified in crabs, salmon, flamingo feathers, certain algae such as *Haematococcus pluvialis*, and fungi [2]. Astaxanthin can be obtained through direct extraction or biosynthesis. Due to its potent antioxidant capacity, by exceeding vitamin E by over 100 times and β-carotene by 100 times in antioxidant activity, it finds applications across multiple fields [3]. In medicine, research indicates astaxanthin may inhibit cancer cell growth, proliferation, and metastasis through various mechanisms, while also aiding in treating neurodegenerative diseases, such as Parkinson's syndrome and Alzheimer's disease) and preventing atherosclerosis. In skincare, astaxanthin effectively quenches free radicals induced by UV radiation, preventing photoaging and reducing UVA/UVB damage to the skin. Consequently, it is incorporated into various cosmetic products including moisturizers, anti-wrinkle eye creams and face masks [4]. Thus, most applications of astaxanthin are based on its unique properties. This paper

comprehensively discussed its application in combating exercise fatigue by focusing on these characteristics.

2. Chemical structure and properties of astaxanthin

Astaxanthin ($C_{40}H_{52}O_4$) has a molecular weight of 596.86 and belongs to the class of terpenoid unsaturated compounds.

Schematic representation of astaxanthin's chemical structure



At its core lies a chain structure composed of 11 conjugated double bonds, with a β-violane ring at each end. These rings bear a hydroxyl group (–OH) and a ketone group (C=O), respectively. This long-chain conjugated double bond system accounts for astaxanthin's deep pink or red coloration and forms the basis of its potent antioxidant activity. Regarding stereochemistry, astaxanthin possesses two chiral centers (C-3 and C-3'), resulting in three stereoisomers: 3S,3'S, 3R,3'R, and 3R,3'S. Natural astaxanthin primarily originates from *Haematococcus pluvialis*, predominantly in the 3S,3'S configuration, which exhibits the strongest antioxidant activity [5]. The properties of astaxanthin are largely derived from its structure. Its potent antioxidant capacity stems primarily from its long conjugated double bond system, which stabilizes free radical intermediates, while the terminal hydroxyl and ketone groups also participate in radical quenching. *In vivo*, the reaction between peroxynitrite anion and hydrogen peroxide generates hydroxyl radicals, which can destroy red blood cells and degrade DNA, cell membranes, and polysaccharides. As the number of conjugated double bonds in astaxanthin increases, its ability to quench reactive oxygen species also strengthens. Additionally, the reactivity of the polar hydroxyl configuration in carotenoids is restricted when integrated into the membrane bilayer, hindering reactions between their polyene chains and singlet oxygen. Therefore, astaxanthin, which simultaneously contains hydroxyl and ketone groups, exhibits higher antioxidant activity. The ketone group in astaxanthin activates the hydroxyl group and promotes hydrogen transfer to peroxyl radicals, enhancing its antioxidant potency. Ketone groups at positions 4 and 4' further boost astaxanthin's antioxidant properties. By effectively scavenging free radicals and reducing oxidative stress, astaxanthin indirectly suppresses inflammatory responses and enhances immune cell function. In recent years, ongoing research into the structural characteristics of astaxanthin has yielded continuous progress in its application within the field of exercise science. Its antioxidant, anti-inflammatory, and free radical scavenging mechanisms have been progressively validated, with further in-depth studies conducted in related areas.

3. Mechanism of astaxanthin in alleviating exercise fatigue

Exercise-induced fatigue represents a complex physiological response triggered by physical exertion, whose underlying mechanisms can be analyzed at both central and peripheral levels. Central fatigue primarily stems from functional inhibition of motor neurons from the brain to the spinal cord, closely linked to altered neurotransmitter balance: Prolonged exercise increases free tryptophan in the blood, elevating serotonin (5-HT) levels in the

brain, which induces drowsiness and reduces exercise drive. simultaneously, reduced levels of excitatory neurotransmitters like dopamine (DA) further diminish the central nervous system's mobilization capacity [6]. Additionally, substances such as ammonia produced by muscle metabolism entering brain tissue may interfere with neural transmission, exacerbating central inhibition. Peripheral fatigue occurs at the neuromuscular junction and within skeletal muscle cells, primarily involving energy depletion and metabolic byproduct accumulation: For instance, excessive depletion of phosphocreatine (CP) and muscle glycogen impairs ATP resynthesis, while the intracellular acidic environment caused by lactic acid accumulation inhibits key enzyme activity (e.g., phosphofructokinase) and disrupts calcium ion release and recycling in the sarcoplasmic reticulum, ultimately reducing muscle contractility [7]. Furthermore, oxidative stress resulting from free radical attacks on cell membrane structures damages muscle cell integrity, exacerbating fatigue.

3.1. Antioxidant mechanisms

Astaxanthin regulates oxidative stress (OS) in the body. Oxidative stress refers to an imbalance between the production of reactive oxygen species (ROS) and the body's antioxidant capacity. Under normal conditions, ROS production and consumption maintain a dynamic equilibrium. During intense exercise-induced oxidative stress, intracellular ROS generation exceeds clearance capacity. Excessive ROS attack critical biomolecules, with lipid peroxidation damage being particularly prominent. This directly compromises the integrity of cell membranes and various organelles, leading to functional impairment [8]. Furthermore, excessive ROS disrupts the normal release and recycling of calcium ions (Ca^{2+}) in the sarcoplasmic reticulum and reduces the sensitivity of troponin to Ca^{2+}. The direct consequence is decreased muscle fiber contraction efficiency and reduced maximum voluntary contraction force [9]. Simultaneously, ROS accumulation induces vasoconstriction, reducing blood flow to active muscle tissue. This not only limits oxygen (O_2) delivery but also impedes the timely supply of energy substrates like glucose and fatty acids. Consequently, ATP resynthesis rates fail to meet exercise demands, accelerating fatigue onset [10]. Astaxanthin possesses potent antioxidant capacity due to its unique molecular structure. Its exceptional antioxidant activity primarily stems from its distinctive molecular composition ($C_{40}H_{52}O_4$). Its long-chain conjugated double bond system and terminal hydroxyl (–OH) and ketone (–C=O) groups efficiently scavenge large amounts of reactive oxygen species (ROS) generated during exercise and quench singlet oxygen. This terminates free radical chain reactions, protecting muscle cell membranes and mitochondrial structures from oxidative damage while maintaining cellular integrity [11]. Furthermore, astaxanthin activates the body's intrinsic "antioxidant defense mechanism" by regulating oxidative stress through the Nrf2 signaling pathway. Under basal conditions, Nrf2 binds to its inhibitory protein Keap1 in the cytoplasm and undergoes continuous degradation, rendering it inactive. Astaxanthin intervention alters Keap1's conformation, causing it to dissociate from Nrf2. The dissociated Nrf2 is then transported into the cell nucleus. Within the nucleus, Nrf2 binds to antioxidant response elements (AREs), initiating transcription and expression of downstream key antioxidant enzyme genes including heme oxygenase-1 (HO-1), superoxide dismutase (SOD), and catalase (CAT) [12]. This process activates the cell's intrinsic "antioxidant army", enhancing the body's capacity to scavenge reactive oxygen species (ROS) and mitigate lipid peroxidation damage, ultimately counteracting oxidative stress.

3.2. Anti-inflammatory mechanism

During moderate-to-high-intensity exercise, particularly exhaustive or unaccustomed eccentric movements (e.g., downhill running, strength training), muscle fibers undergo Z-disk rheological changes, and physical tears occur in

the sarcolemma and extracellular matrix [13]. Damaged cells immediately release a series of "alarm signals", pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β). These signals activate vascular endothelial cells, increase vascular permeability, and attract circulating neutrophils (the first immune cells to arrive at the injury site) to rapidly infiltrate the damaged muscle tissue. Subsequently, macrophages are recruited. Initially presenting as pro-inflammatory M1 macrophages, they phagocytose cellular debris and release additional cytokines (e.g., TNF-α, IL-1β, IL-6), amplifying inflammatory signals to thoroughly clear the injured area. Multiple inflammatory biomarkers have been identified, including cytokines, chemokines, immune-related effectors, acute phase proteins (APPs), reactive oxygen and nitrogen species (RONS), platelet-activating factor (PAF), prostaglandins and cyclooxygenase-related factors (including transcription factors and growth factors), as well as signaling pathways such as NF-κB, MAPK, and JAK-STAT [14]. Studies indicate that astaxanthin suppresses the production of inflammatory mediators in LPS-stimulated BV-2 microglia by inhibiting the induction and proteolytic degradation of iNOS and COX-2 [15]. Park et al. found that in streptozotocin-induced diabetic rat models, astaxanthin reduced COX-2, iNOS, and ICAM-1 protein expression levels by alleviating inflammatory responses [16]. In a study by Baralic et al., two groups of soccer players were supplemented with astaxanthin or a placebo. Over time, the placebo group exhibited increases in total white blood cell count, neutrophil count, and hs-CRP levels, while no such changes were detected in the supplement group. This further supports the notion that Asx, as a dietary supplement, possesses the ability to suppress mild inflammatory events induced by training [17].

3.3. Mitochondrial protection mechanism

The core function of mitochondria is ATP synthesis via oxidative phosphorylation. When mitochondria are damaged, their inner membrane structures, cristae will swell and rupture, leading to uncoupling of oxidative phosphorylation or a sharp decline in its efficiency. This means nutrients are consumed without efficient ATP production. Simultaneously, the activity of the key enzyme responsible for ATP synthesis, the H^+-ATPase (or F0F1-ATP synthase) also declines [18]. Consequently, working muscles cannot obtain a sustained, adequate energy supply, leading to weakened contraction force and rapid onset of fatigue. Cao Xiuming et al. conducted an experiment using astaxanthin to protect mitochondria damaged by hydrogen peroxide in vitro. They observed the activity of mitochondrial Complex I and ATPase; mitochondrial membrane potential, membrane fluidity, and the degree of mitochondrial permeability transition pore (PTP) opening. Results demonstrated that astaxanthin significantly enhanced the activity of H^+-ATPase (F0F1-ATP synthase) in damaged mitochondria, thereby safeguarding ATP synthesis efficiency [19]. Mitochondria serve as cellular powerhouses, primarily functioning through oxidative phosphorylation via the electron transport chain (ETC) to synthesize ATP. During this process, oxygen acts as the final electron acceptor, being reduced to form water. However, some oxygen molecules undergo incomplete reduction, generating byproducts such as reactive oxygen species (ROS) [20]. Studies indicate that astaxanthin effectively inhibits lipid peroxidation reactions in biological membranes. Furthermore, experimental evidence demonstrates that exogenously added astaxanthin can be taken up by cells and specifically accumulated within mitochondria. Given that key protein complexes of the electron transport chain are primarily embedded in the inner mitochondrial membrane, this distribution characteristic of astaxanthin enables it to effectively mitigate oxidative damage to mitochondrial membrane structures caused by ROS [21]. Astaxanthin effectively mitigates the destructive effects of mitochondrial overload, demonstrating protective effects against oxidative damage across multiple animal models. Studies indicate that in rodents following intense exercise, astaxanthin significantly reduces skeletal muscle damage while decreasing oxidative modification of muscle proteins [22]. Furthermore,

under experimental conditions combining a high-fat diet with treadmill exercise, astaxanthin further suppressed the expression of inflammatory markers [23]. Collectively, these findings indicate that during physiological stress (such as exercise or metabolic load) leading to mitochondrial overload, astaxanthin exerts its antioxidant effects by inhibiting excessive ROS production, thereby protecting mitochondrial structural and functional integrity.

4. Astaxanthin as a therapeutic approach for exercise-induced fatigue

Multiple studies indicate that daily doses of astaxanthin ranging from 4 to 20 milligrams are well-tolerated with no significant side effects. It effectively scavenges excess free radicals generated during exercise, mitigating oxidative stress damage to muscle cells, thereby aiding fatigue relief and accelerating recovery. Additionally, both short-term higher doses (e.g., 100 mg/day) and long-term moderate doses (8–12 mg/day) are considered safe [24–26]. Baralic I et al. demonstrated that astaxanthin supplementation (4 mg/day for 90 days) reduced creatine kinase (CK) release, decreased reactive oxygen species (ROS) production, and enhanced overall antioxidant status in young soccer players [27]. Daniel et al. found that 12 mg/day of astaxanthin supplementation in cyclists, for 7 days improved cycling performance while promoting short-term energy metabolism and increasing fat oxidation rates [28].

Currently, combined interventions may demonstrate superior effects compared to single-agent astaxanthin applications. Combined interventions represent a research hotspot, exemplified by the combination of astaxanthin and hyperbaric oxygen therapy. A 2024 study on rugby players demonstrated that post-exhaustion exercise, hyperbaric oxygen therapy combined with astaxanthin supplementation (60 minutes of hyperbaric oxygen after oral administration of 16 mg astaxanthin) more effectively promoted recovery of muscle oxygen saturation (SmO_2) and accelerated clearance of blood lactate (Bla) compared to hyperbaric oxygen alone or natural recovery. During hyperbaric oxygen therapy, factors like elevated oxygen concentration may exacerbate oxidative stress. Astaxanthin's potent antioxidant properties counteract this side effect, creating a complementary effect. Animal studies further suggest that the astaxanthin-hyperbaric oxygen combination may enhance the body's intrinsic antioxidant defenses by modulating the Keap1/Nrf2/HO-1 signaling pathway, providing a deeper theoretical basis for the synergistic intervention [29].

To date, encapsulation techniques such as spray drying have enabled the production of water-soluble astaxanthin powder, which can be added to sports drinks as a novel approach to alleviating exercise-induced fatigue. By combining electrolytes, vitamins, and other nutrients, this approach integrates nutritional supplementation with anti-fatigue effects. It not only effectively replenishes athletes' fluids, carbohydrates, and electrolytes but also scavenges exercise-induced free radicals, alleviating exercise-induced fatigue and enhancing athletic performance efficiency.

5. Summary and outlook

This paper systematically reviews the mechanisms and application prospects of astaxanthin in alleviating exercise-induced fatigue, based on existing research and its unique chemical structure and biological properties. The onset of exercise fatigue involves complex imbalances in central regulation and peripheral metabolism, where oxidative stress, inflammatory responses, and mitochondrial dysfunction are key factors accelerating fatigue progression. Through a dual mechanism of "directly scavenging reactive oxygen species" and "activating the Keap1/Nrf2 pathway to enhance endogenous antioxidant enzymes", astaxanthin effectively mitigates exercise-induced oxidative stress. Simultaneously, it suppresses the NF-κB signaling pathway, downregulating the expression of

inflammatory mediators such as TNF-α and IL-1β to control excessive inflammatory responses. Furthermore, astaxanthin specifically accumulates in mitochondria, stabilizing membrane potential, protecting electron transport chain function, and enhancing ATP synthesis efficiency. This synergistic action across three critical dimensions, the antioxidant defense, anti-inflammation, and energy supply, comprehensively alleviates exercise-induced fatigue. However, despite astaxanthin's promising potential for improving exercise fatigue, several issues warrant further exploration in future studies.

While existing studies have established a general effective dosage range (e.g., 4–20 mg/day), the optimal supplementation dosage and duration for different sports disciplines, intensity levels, and individual variations, such as training status and physical constitution remain unclear. Future studies require more refined clinical trials to establish personalized supplementation protocols. Concurrently, astaxanthin's inherent poor water solubility and low stability remain bottlenecks limiting its bioavailability. While microencapsulation techniques have advanced, developing novel, more targeted, and stable nano-delivery systems, such as liposomes or polymeric nanoparticles will be crucial for enhancing efficacy and improving human utilization rates. Finally, most current research focuses on animal models or small sample populations, lacking large-scale, randomized double-blind, multicenter clinical evidence. Future studies require higher-level clinical data to robustly support the application value and safety of astaxanthin in sports medicine.

Disclosure statement

The author declares no conflict of interest.

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