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Benefits of Astaxanthin Supplementation: Selected Issues

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ABSTRACT:

INTRODUCTION: Astaxanthin, a carotenoid compound belonging to the xanthophyll group, occurs naturally in algae, yeast, and marine organisms such as shrimp, trout, lobster, and krill. Renowned for its antioxidant prowess, astaxanthin shields mitochondria from harm caused by reactive oxygen species (ROS). Its exceptional antioxidant potency is noteworthy, surpassing that of α-tocopherol (Vitamin E) by 100-fold and eclipsing over 600 other recognized natural carotenoids.

REVIEW METHODS: The article was complied by analyzing data from PubMed and Google Scholar data regarding the benefits of astaxanthin supplementation.

THE STATE OF KNOWLEDGE: Astaxanthin, offers a range of health benefits. It modulates immune responses, inhibits cancer cell growth, reduces bacterial presence and gastric inflammation. With potent antioxidant properties, it also serves as a neuroprotective agent by combating neuroinflammation. Additionally, astaxanthin shows promise in preventing and treating liver diseases, thanks to its antioxidant, anti-inflammatory, and signaling pathway

regulation properties. Overall, antioxidants like astaxanthin, whether from diet or supplements, help combat lipid and protein oxidation, thereby slowing down the progression of atherosclerosis.

CONCLUSION: Astaxanthin emerges as a promising candidate for treating various pathological conditions linked to oxidative damage and impaired mitochondria function. These conditions span across cardiovascular diseases, neurodegenerative disorders and liver diseases. It could also help healthy people like athletes in enhancement of overall quality of life.

Keywords: Astaxanthin; carotenoids; inflammation; oxidative stress; mitochondria; neuroprotection; cardiovascular system; liver disease

1.INTRODUCTION

Astaxanthin is a carotenoid molecule belonging to the xanthophyll group, naturally occurring in algae, yeast and marine animals such as shrimps, trout, lobster and krill. Its application is broad, encompassing both biological and physiological effects. [1]

Studies have indicated that astaxanthin preserving the structural and functional integrity of mitochondria is crucial for normal cellular function. Mitochondria are central to energy metabolism, maintaining cellular redox balance and regulating apoptosis. Astaxanthin has antioxidant properties and protecting mitochondrial from damage caused by reactive oxygen species (ROS).

ROS are common by-products generated during energy metabolism. Cells must tightly regulate ROS levels to prevent their detrimental binding and inactivation of essential biomolecules such as proteins, DNA, RNA, lipids, and signaling molecules.[2]

Astaxanthin is distinguished as an exceptionally powerful antioxidant, with activity surpassing α-tocopherol (Vitamin E) by 100-fold, as well as exceeding over 600 other recognized natural carotenoids. Furthermore, astaxanthin exhibits a wide array of beneficial effects, including anti-inflammatory, anti-obesity, anti-apoptotic, anti-hypertensive, antimicrobial, neuroprotective, gastroprotective and antitumoral activities. [3]

2. REVIEW METHODS: The article was complied by analyzing data from PubMed and Google Scholar data regarding the benefits of astaxanthin supplementation.

3.THE STATE OF KNOWLEDGE

3.1 IMPACT ON INFLAMMATION

Astaxanthin is involved in modulating immune responses, impedes the proliferation of cancer cells, diminishes bacterial presence and gastric inflammation, and provides defense against oxidative stress induced by UVA radiation. Immune cells, characterized by a high proportion of polyunsaturated fatty acids in their plasma membranes, are particularly vulnerable to oxidative stress. They tend to generate an excess of reactive oxygen and nitrogen species, which, when unchecked, can disrupt the delicate balance between oxidants and antioxidants, leading to damage to cell membranes, proteins, and DNA. [4] AST (astaxanthin) diminishes the formation of reactive oxygen species (ROS) by upregulating the expression of enzymes responsive to oxidative stress, including superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx). Alongside elevated ROS levels, M1 macrophages produce a diverse array of pro-inflammatory mediators.

AST's antioxidant and anti-inflammatory actions are evident in clinical and experimental research, characterized by its ability to decrease the production of cytokines like tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6) and interleukin-1β (IL-1β). Moreover, AST exerts anti-inflammatory effects by inhibiting the enzyme cyclooxygenase-1 (COX-1) and modulating nitric oxide (NO) levels. [5] Research has demonstrated that astaxanthin effectively inhibits the release of cytochrome c caused by mitochondria permeabilization, consequently preventing mitochondria-mediated apoptotic cell death. Additionally, astaxanthin treatment safeguards both the inner and outer membranes of mitochondria and the cristae, from structural damage induced by substances like H2O2 or bleomycin, while also enhancing mitochondrial membrane potential (MMP). AST activates p53 activation, suppresses STAT3 activity, and attenuates inflammatory mediators induced by damage. Moreover, AST impredes NF-κB diminishing the production of inflammatory factors through antioxidant pathways. Notably, IL-6 as a pivotal target for AST's anti-inflammatory action and disrupts the positive feedback loop of inflammatory factors, thus averting the onset of inflammatory storms. [6]

Effect of astaxanthin on oxidative stress-associated diseases and mitochondrial dysfunction. [7, 8]

Increase	Decrease
Cell viability MMP (mitochondrial membrane potential) Mitochondrial membrane integrity SOD Catalase activities	Apoptosis Development and progression diseases Cytotoxicity Mitochondial swelling, fragmentation, permeabilization Pro-apoptotic protein Production ROS (reactive oxygen species), which induce cellular dysfunction and cell death Histopatological changes NF-κB (nuclear factor-κB), Oxidative stress marker (MDA) interleukin-1β (IL-1β), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α)

Astaxanthin plays a crucial role in boosting the immune response, and is a multi-target pharmacological carotenoid that helps in treating neurological disorders such as Parkinson's disease (PD), Alzheimer's disease, depression, aging, and brain and spinal cord injuries. [9] Accordingly, oxidative stress is critical in the development and progression of inflammatory diseases, cardiovascular diseases, liver diseases, and metabolic syndromes including diabetes [10] as well as aging.

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, cardiovascular diseases and cancer. Benefits on skin and eye health promotion have also been reported, highlighting its potential for the prevention of skin photo-aging and the treatment of eye diseases like glaucoma, cataracts and uveitis. [11]

3.2 IMPACT ON NEUROLOGICAL DISORDERS

Neuroinflammation functions as a defense mechanism to protect the central nervous system from different insults; however, it is also a pathological hallmark of numerous neurological and neurodegenerative diseases. Astaxanthin, a natural carotenoid with marked antioxidant capacity, suppresses neuroinflammation and is thus neuroprotective. First and foremost, astaxanthin can effectively combats oxidative stress-induced cell injury and death known to

trigger neuroinflammation, in part, by inhibiting the production of pro-inflammatory cytokines via the NF-κB and MAPK pathways. It can also potentially modulate neuroinflammation in the brain by maintaining the integrity of the BBB and alleviating peripheral inflammation. [12]

AST has been demonstrated to stimulate axonal regeneration and improve motor function by activating the cAMP/PKA/CREB signaling pathway [56]. Supplementation with AST during acute cerebral infarction (ACI) resulted in reduced oxidative stress and downregulation of mRNA expression for brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF), leading to functional enhancement. Additionally, AST exhibited a protective effect against oxidative damage in cerebral ischemia-reperfusion injury (IRI) [58]. AST exerts these beneficial effects, at least partially, through the PI3K/Akt/GSK3β/Nrf2 signaling pathway, consistent with the attenuation of apoptosis induced by oxygen and glucose deprivation (OGD) in models of cerebral ischemia-induced apoptosis[13].

ALZHEIMER'S DISEASE

Alzheimer's disease (AD), a degenerative neurological condition marked by cognitive decline and memory loss, may result from disruptions in the cortical environment, including oxidative stress, inflammation, and the accumulation of β-amyloid plaques. [14]

An excessive buildup of β-amyloid protein (Aβ) in the cerebral cortex and hippocampus stands out as a prominent characteristic of AD. Aβ contributes to the generation of oxidative stress by generating reactive oxygen and nitrogen species [19]. This oxidative stress production is associated with numerous detrimental effects, including the formation of neurofibrillary tangles, inflammation, apoptosis, protein oxidation, and lipid peroxidation. These disruptions can lead to a decline in cognitive functions due to significant damage to neural connections between the cerebral cortex and the hippocampus [15].

PARKINSON'S DISEASE

Parkinson's disease (PD) ranks as the second most prevalent neurodegenerative condition among the elderly. Key clinical manifestations of PD encompass resting tremor, muscle rigidity, postural instability, and freezing, along with non-motor symptoms like anosmia, constipation, sleep disturbances, and depression [16].

PD is characterized by the loss of dopaminergic neurons in the midbrain, the formation of α-synuclein aggregates known as Lewy bodies, and the impairment of non-dopaminergic pathways, resulting in both motor and non-motor dysfunction.

AST regulated ROS-dependent oxidative damage and mitochondrial dysfunction and also attenuated PI3K/AKT and MAPK protein kinase pathways, thereby addressing neurological disorders such as PD [17].

NEUROPATHIC PAIN

NP involves multiple destructive signaling pathways and mechanisms, predominantly implicating neuromodulators such as glutamate, NR2B, gamma-aminobutyric acid (GABA), serotonergic, and noradrenergic systems, along with inflammatory agents like cytokines, prostaglandins, and reactive oxygen species [20]. These factors influence the activation of microglia and astrocytes, ion channel dynamics, neuronal excitability, and even apoptotic processes. They found that AST decreased astrocytic activation. AST prevented the increase in IL-6, IL-1β, and TNF-α in the spinal cord and hippocampus. In summary, AST is presented as a promising therapeutic option for addressing NP. [18].

3.3 IMPACT ON LIVER DISEASES

Astaxanthin has been employed for both prevention and treatment across a range of systemic diseases in vivo owing to its diverse biological activities. Research indicates that astaxanthin exerts significant preventive and therapeutic effects on conditions such as liver fibrosis, non-alcoholic fatty liver disease, liver cancer, drug-induced liver injury, and ischemia-induced liver injury.

Its mechanisms of action are associated with antioxidant and anti-inflammatory properties, as well as the regulation of multiple signaling pathways [21].

LIVER FIBROSIS

Liver fibrosis is a common occurrence in the progression of chronic liver diseases, regardless of their underlying causes, which may include viral hepatitis infection, alcohol abuse, and metabolic-associated fatty liver disease (MAFLD). It is typically associated with liver injury, inflammation, and cell death. The abnormal buildup of extracellular matrix (ECM) components, such as collagens and alpha-smooth muscle actin proteins, expressed by liver myofibroblasts, serves as markers of hepatic fibrogenesis. Hepatic stellate cells (HSCs), once activated, become a major source of myofibroblasts in liver fibrosis. Despite numerous drugs undergoing clinical trials, there are currently no treatments for liver fibrosis approved by the Food and Drug Administration (FDA) [22].

Evidence suggests that:

- astaxanthin improved liver fibrosis induced by CCL4 and BDL;
- astaxanthin suppressed the activation of HSCs both in vivo and in vitro;

- astaxanthin hindered HSCs activation by reducing the expression of NF-κB and TGF-β1, while preserving the balance between MMPs and TIMPs;
- astaxanthin potentially impacts the energy metabolism in HSCs by downregulating autophagy levels [23].

NON- ALCOHOLIC FATTY LIVER DISEASE

Non-Alcoholic Fatty Liver Disease (NAFLD) stands out as the leading cause of chronic liver disease in developed countries. According to the American Association for the Study of Liver Diseases (AASLD), NAFLD is characterized by the excessive accumulation of fat in the liver, as confirmed by histology or radiological imaging. Key criteria include no significant alcohol consumption, absence of other underlying liver conditions, and no competing causes for hepatic fat accumulation. The surge in NAFLD prevalence in industrialized nations is closely linked to rising rates of obesity and metabolic syndrome, which encompass conditions like hypertension, type 2 diabetes (T2DM), and dyslipidemia [24]. Many guidelines advocate for the intake of micronutrients known for their antioxidative and anti-inflammatory properties as a preventive and therapeutic measure for NAFLD [25]. Astaxanthin inhibits the activation of hepatic stellate cells, thus suppressing the overexpression of genes involved in fibrosis by disrupting the transforming growth factor-β/Smad3 signaling pathway [26]. Moreover, it mitigates diet-induced obesity and the accumulation of lipids in the liver, while also improving insulin resistance induced by oxidative stress through enhancing insulin signaling and inhibiting pro-inflammatory pathways [27].

Astaxanthin also mitigated hepatocyte damage and restored mitochondrial function in NAFLD by enhancing the FGF21/PGC-1α pathway. This indicates that astaxanthin holds promise as a potential treatment or alleviation for NAFLD [28].

3.4 IMPACT ON CARDIOVASCULAR SYSTEM

Oxidative stress and inflammation are recognized as established risk factors for cardiovascular health, supplementing traditional factors such as family history, hypertension, hyperlipidemia and smoking [31]. Consequently, antioxidant therapies such as vitamin E, C, and β-carotene have been evaluated in clinical trials with patients at risk of cardiovascular events [29]. Antioxidants, present in both dietary sources and supplements, function to diminish lipid and protein oxidation, consequently decelerating the advancement of atherosclerosis. The correlation between antioxidant intake, plasma levels, and the decrease in cardiovascular events provides additional evidence for the involvement of oxidative stress in the genesis of vascular

diseases associated with atherosclerosis. Studies investigating the dietary consumption or supplementation of β-carotene and vitamin E consistently demonstrate a correlation between higher levels and reduced risk of cardiovascular disease [30].

Carotenoids exhibit diverse effects depending on their polarity and, consequently, their interaction with cellular membranes. Lycopene and β-carotene, being non-polar, disrupt the membrane structure and promote lipid oxidation in models enriched with polyunsaturated fatty acids, whereas polar astaxanthin maintains membrane integrity [32].

Astaxanthin exhibits strong antioxidant properties, effectively neutralizing free radicals and reactive oxygen and nitrogen species. It is 11 times more effective at quenching singlet oxygen than β-carotene and 550 times more potent than alpha tocopherol [33]. Its remarkable potency and polar characteristics render astaxanthin a promising nutraceutical for continued exploration in atherosclerotic cardiovascular disease, where cellular protection by antioxidants may offer clinical advantages [45].

Astaxanthin exists in three stereoisomeric forms: (3-R,3′-R), (3-R,3′-S), and (3-S,3′-S) [34]. Disodium disuccinate astaxanthin (DDA) is a synthetic astaxanthin comprising a blend of all three stereoisomers, in a ratio of 1:2:1. DDA was developed by Cardax Pharmaceuticals and utilized in animal studies exploring myocardial ischemia-reperfusion injury models. This variant of astaxanthin was praised for its superior aqueous solubility, unlike other carotenoids, allowing for both oral and intravenous administration. Although DDA is no longer in production, the same company now manufactures a second synthetic astaxanthin compound: Heptax/XanCor, CDX-085 [35].

The company asserts that it is formulated for thrombotic protection, triglyceride reduction, metabolic syndrome, and inflammatory liver disease [37]. Moreover, it boasts increased water dispersibility and enhanced bioavailability compared to natural astaxanthin and DDA. Synthetic forms are metabolized via hydrolysis in the intestine, releasing free astaxanthin for absorption [36].

Astaxanthin is a powerful antioxidant, and given its physicochemical properties and the findings from preliminary experimental studies in ischemia-reperfusion models of cardiovascular disease, it merits consideration for testing in human clinical trials [46]. Thus far, there have been no safety concerns observed in human clinical studies where astaxanthin has been administered. Because astaxanthin is a potent antioxidant and is linked to membrane preservation, it may shield against oxidative stress and inflammation, offering cardiovascular advantages [38].

A RANDOMIZED TRIAL INVESTIGATING THE IMPACT OF ANTIOXIDANT SUPPLEMENTATION ON EXERCISE-INDUCED CARDIAC TROPONIN RELEASE IN CYCLISTS

Cardiac troponin serves as the biochemical gold standard for diagnosing acute myocardial infarction [39]. However, it's noteworthy that elevated concentrations of cardiac troponin are often observed during and after endurance-type exercise. Oxidative stress linked with prolonged exercise has been suggested as a contributor to the release of cardiac troponin. Hence, the objective of this study was to evaluate the impact of a 4-week supplementation with astaxanthin on antioxidant capacity and exercise-induced cardiac troponin release in cyclists[40]. During the cycling trial conducted prior to supplementation, there was a notable increase in median cardiac troponin T concentrations from 3.2 (IQR 3.0–4.2) to 4.7 ng/L (IQR 3.7–6.7) immediately post-exercise ($p < 0.001$). Following four weeks of astaxanthin supplementation, the mean basal plasma astaxanthin concentrations significantly rose from undetectable levels to 175±86 μg·kg−1. Nevertheless, daily astaxanthin supplementation did not impact exercise-induced cardiac troponin T release ($p = 0.24$), as evidenced by the incremental area under the curve. Moreover, the elevation in basal plasma astaxanthin concentrations did not elicit changes in antioxidant capacity markers (trolox equivalent antioxidant capacity, uric acid, and malondialdehyde). Neither inflammation markers (high-sensitivity C-reactive protein) nor exercise-induced skeletal muscle damage (creatine kinase) were affected by astaxanthin supplementation [40,41].

A PILOT STUDY ON CARDIAC FUNCTION IN HEART FAILURE PATIENTS WITH LEFT VENTRICULAR SYSTOLIC DYSFUNCTION

In a prospective pilot study, heart failure (HF) patients with left ventricular (LV) systolic dysfunction were included to investigate potential improvements in cardiac function and exercise tolerance attributed to the suppression of oxidative stress via 3-month astaxanthin supplementation [42]. Prior to and following the supplementation period, various markers of oxidative stress—including serum Diacron reactive oxygen metabolite (dROM), biological antioxidant potential (BAP), and urinary 8-hydroxy-2′-deoxyguanosine (8-OHdG) concentrations—along with LV ejection fraction (LVEF) and 6-minute walk distance (6MWD) were evaluated. Subsequently, data from 16 HF patients were analyzed. Results revealed a significant decrease in dROM levels from 385.6 ±82.6 U.CARR to 346.5 ±56.9 U.CARR ($p = 0.041$) following the 3-month astaxanthin supplementation, with no notable changes observed in BAP and urinary 8-OHdG levels. Additionally, LVEF increased from 34.1 ±8.6% to 38.0 ± 10.0% ($p = 0.031$), and 6MWD improved from 393.4 ±95.9 m to 432.8 ±93.3 m ($p = 0.023$).

Notably, significant associations were identified between the percentage changes in dROM levels and those in LVEF.

The results of this recent prospective, small-scale, uncontrolled investigation offer several fresh insights into the impact of astaxanthin supplementation on patients with HF. Firstly, an elevated baseline level of oxidative stress, indicated by an increase in dROM levels, correlated with impaired LV systolic function at the outset. Secondly, a 3-month regimen of daily oral astaxanthin supplementation notably raised the blood concentration of astaxanthin in HF patients. Thirdly, the dROM findings revealed a reduction in blood oxidative stress following the 3-month supplementation, while 8-OHdG results showed no corresponding decrease in urinary oxidative stress. Fourthly, a positive relationship was observed between the baseline level of oxidative stress and the extent of reduction in blood oxidative stress. Furthermore, serum inflammatory markers remained unchanged post-supplementation [44]. Sixthly, an improvement in LV systolic function was observed after the 3-month supplementation, accompanied by enhanced exercise tolerance. Lastly, noteworthy correlations were found between the reduction in oxidative stress and improvements in both LV systolic function and LV remodeling [43]. These findings suggest that a 3-month regimen of astaxanthin supplementation may enhance LV systolic function and exercise tolerance, possibly through the alleviation of oxidative stress [42, 44].

CONCLUSION

Astaxanthin can effectively mitigate oxidative stress generated under various pathological conditions and prevent oxidative stress-induced mitochondrial dysfunction. Maintaining structural and functional integrity of the mitochondria can avert the onset and/or progression of human diseases. Astaxanthin can be considered as a potential therapeutic agent for treatment of pathological conditions associated with excess oxidative damage and dysfunctional mitochondria. Such conditions occur in several inflammations as also neurological disorders, cardiovascular problems, liver diseases including NAFLD, however astaxanthin could help healthy people like athletes in enhancement of overall quality of life.

Disclosures

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