# REVIEW

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## ASTAXANTHIN AS AN ANTIOXIDANT: EXPLORING ITS POTENTIAL IN PREVENTION OF MITOCHONDRIAL DYSFUNCTION

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*Astaxanthin is a natural carotenoid with a powerful antioxidant activity, high stability and the ability to cross both the blood-brain and the blood-retinal barriers. It demonstrates significant potential in mitigating diseases related to oxidative stress. Mitochondria are the organelles most susceptible to molecular damage caused by oxidative stress, Transcriptional pathways regulated by Nrf2 and PGC-1 play the crucial role in maintaining mitochondrial function and biogenesis. In this review the molecular mechanism of astaxanthin influence on Nrf2 and PGC-1α pathways and cellular health are analysed.*

*K e y w o r d s: astaxanthin, mitochondria, oxidative stress, Nrf2 and PGC-1 transcriptional pathways.*

Oxidative stress is a primary mechanism that accelerates aging and contributes to the pathogenesis of various degenerative diseases [1]. Understanding the relationship between oxidative stress and aging provides a foundation for developing interventions that can promote healthy aging, enhance overall well-being and reduce the risk of chronic disease development [1]. Mitochondria are essential in the aging process due to their roles in bioenergetics, oxidative stress management, and the regulation of cell death [2]. Mitochondria are the powerhouses of cellular life, providing not only energy but also regulating essential processes such as apoptosis and metabolism [3, 4]. Mitochondrial dysfunction can lead to significant damage, which underlies many degenerative diseases, including neurodegenerative disorders, cardiovascular diseases, diabetes, and cancer [5]. Understanding the role of mitochondria and developing strategies to protect or restore their function are crucial steps in preventing and treating degenerative diseases as well as addressing the effects of aging [6]. However, mitochondria are also susceptible to damage from oxidative stress and metabolic disturbances. The Nrf2 and PGC-1α pathways play vital roles in maintaining mitochondrial function by regulating the response to oxidative stress and supporting mitochondrial biogenesis [3, 4, 8].

The negative effects of free radicals can be mitigated by antioxidants, whether produced by the body or obtained from food and supplements, so antioxidants can be used as an effective strategy. [1, 8]. Astaxanthin is a naturally occurring carotenoid compound that exhibits exceptionally high antioxidant activity [9, 10]. Its unique structure makes it highly effective in reducing oxidative stress and

**List of abbreviations.** AST – Astaxanthin; ROS – reactive oxygen species; Nrf2 – nuclear factor erythroid 2- related factor 2; PGC-1 – peroxisome proliferator-activated receptor gamma coactivator 1; AMPK – AMP-activated protein kinase; TFAM – transcription factor A mitochondrial; FFA – free fatty acids; OA – oleic acid; PA – palmitic acid; NAFLD – non-alcoholic fatty liver disease; STZ – streptozotocin; OTA – ochratoxin A; IVVD – intervertebral disc degeneration; Aβ – amyloid β; BDNF – brain-derived neurotrophic factor; DMSO – dimethyl sulfoxide.

maintaining cellular health [11, 12]. Astaxanthin has several advantages over other antioxidants: it does not become a prooxidant even at high concentrations [10, 13, 14], it has optimal membrane penetration as it can cross both the blood-brain barrier and the blood-retinal barrier, providing benefits to the brain and eyes, and it is highly stable, with its chemical structure offering long-term protection [11]. Humans cannot synthesize astaxanthin in the body [9]. Astaxanthin (AST) is naturally found in microalgae, fungi, yeast, and marine organisms such as salmon, shrimp, lobster, and krill. It is regarded as a naturally occurring antioxidant with high efficacy [6, 10, 15].

Numerous studies have illustrated the mechanism by which prolonged oxidative stress triggers chronic inflammation, which in turn plays a crucial role in the development of various chronic diseases, including cancer, diabetes, as well as cardiovascular and neurological disorders. The intricate relationship between Nrf2 and PGC-1 has been explored concerning the risk of multiple age-related diseases [15, 16]. This review highlights the biological activities and health benefits of AST, with a specific focus on its role in regulating Nrf2 and PGC-1 signaling pathways.

*Method.* Literature data sources were collected from scientific databases such as PubMed, ScienceDirect, SpringerLink, and Google Scholar using a combination of keywords such as “astaxanthin”, “antioxidant”, “Nrf2”, “PGC-1”, and “mitochondrial biogenesis”. The data taken comes from articles published in the last 10 years and are in English. The literature is classified based on the focus of the study, such as the effects of astaxanthin on Nrf2, PGC-1, and mitochondrial biogenesis, as well as their relevance in the treatment of diseases.

## Astaxanthin: antioxidant poperties and mechanisms

Astaxanthin is found in the microalga *Haematococcus pluvialis*, as well as in yeast, salmon, shrimp, crab and lobster. This carotenoid has significant potential as a nutritional supplement, particularly in mitigating the adverse effects of oxidative stress and inflammation, which contribute to a range of chronic diseases [9, 17, 18]. Astaxanthin possesses a remarkably high antioxidant capacity, demonstrating superior free radical scavenging ability compared to vitamin C (up to 6,000 times) and vitamin E (up to 550 times) [9, 14]. It outperforms vitamins C and E due to its substantially higher antioxidant activity, its capacity to protect cell membranes and the surrounding lipid environment, and its enhanced stability without the risk of becoming a prooxidant. However, the combination of astaxanthin, vitamin C, and vitamin E is often more effective due to their synergistic properties in various bodily environments (hydrophilic and lipophilic). Astaxanthin, which belongs to the xanthophyll carotenoid group, is chemically known as 3,3′-dihydroxy-β, β′-carotene-4,4′-dione. This compound is fat-soluble and possesses unique characteristics that distinguish it from other carotenoids. Astaxanthin has a molecular mass of 596.84 g/mol with the chemical formula $C_{40}H_{52}O_4$. Its molecular structure contains conjugated double bonds at the center, which play a key role in providing antioxidant effects (Figure) [9, 19]. It achieves this by quenching singlet oxygen, neutralizing free radicals, and maintaining membrane integrity by inhibiting lipid peroxidation. For instance, AST’s polyene chain captures free radicals within the cell’s internal membrane, while its terminal ring stabilizes reactive

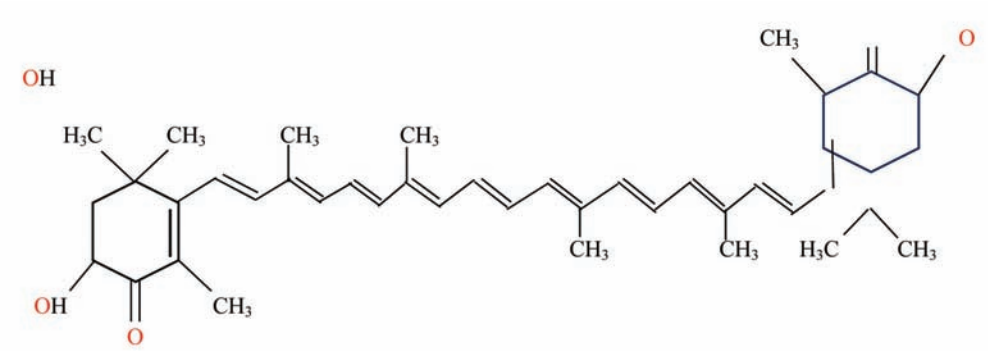


*Figure. Chemical structure of astaxanthin (3,3′-dihydroxy-β, β′-carotene-4,4′-dione)*

molecules on the membrane surface. Additionally, AST minimizes reactive oxygen species (ROS) production by enhancing the expression of oxidative stress-responsive enzymes, including superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase (CAT). Its potent antioxidant properties also play a key role in safeguarding biological systems from excessive oxidative stress, which is often linked to uncontrolled inflammation [16]. Astaxanthin plays a crucial role in reducing ROS production in mitochondria and inhibiting prooxidant enzymes such as NADPH oxidase, which is responsible for ROS production during inflammatory responses. Additionally, AST suppresses the production of inflammatory mediators such as cytokines (e.g., TNF-α, IL-6) and pro-inflammatory enzymes (e.g., COX-2). This multifaceted approach ultimately helps mitigate oxidative stress induced by inflammation [14, 17, 20].

### Astaxanthin enhances mitochondrial biogenesis through Nrf2/PGC-1 pathways

Mitochondrial biogenesis, the process of generating new mitochondria, is a complex and highly regulated mechanism that involve various molecular factors, including Nrf2 and PGC-1 [21, 22]. These factors are essential for enhancing mitochondrial function, maintaining cellular energy balance, and mitigating oxidative stress. Nrf2, a transcription factor renowned for activating genes that counteract oxidative stress through antioxidant response elements (AREs), also plays a crucial role in mitochondrial biogenesis [17, 23]. Furthermore, Nrf2 boosts the production of antioxidant enzymes, such as glutathione peroxidase and superoxide dismutase, thereby reducing oxidative stress and protecting mitochondria from damage caused by ROS [23]. This protective mechanism is critical for preserving mitochondrial function and stability during the biogenesis process. Mitochondrial biogenesis is primarily regulated by PGC-1α [3]. It functions as a transcriptional coactivator, integrating environmental signals with gene expression to enhance mitochondrial capacity. PGC-1α increases the expression of electron transport chain (ETC) enzymes, improves the efficiency of mitochondrial respiration, and enhances oxidative phosphorylation capacity [24, 25]. Additionally, PGC-1α induces Nrf2 and elevates the expression of genes regulated by Nrf2, further protecting mitochondria from oxidative stress [22, 26, 27].

### Astaxanthin's potential for disease treatment through improving mitochondrial function (PGC-1/Nrf2 pathways)

Wu et al. proved that AST reduces hepatocyte damage and mitochondrial dysfunction in non-alcoholic fatty liver disease (NAFLD) by increasing FGF21/PGC-1α expression ($P < 0.05$) [28]. The group of NAFLD encompasses various liver disorders, including steatosis (fat accumulation in the liver), non-alcoholic steatohepatitis (NASH), fibrosis, cirrhosis, and liver cancer (hepatocellular carcinoma). Excessive intracellular lipid accumulation triggers oxidative stress, leading to increased production of ROS, mitochondrial dysfunction, and cytotoxicity. The growth factor FGF21 is an endocrine member of the FGF family and is involved in various metabolic systems. The liver is the primary source of circulating FGF21, with its levels strongly correlated with liver function. Furthermore, clinical studies have shown a relationship between FGF21 and fatty liver disease. Research findings indicate that astaxanthin can reduce lipid accumulation induced by a high-fat diet (HFD) and free fatty acids (FFA), as well as suppress oxidative stress, cell apoptosis, inflammation, and fibrosis in both *in vivo* and *in vitro* studies. Additionally, AST attenuated hepatocyte damage and mitochondrial dysfunction in NAFLD by upregulating FGF21/PGC-1α pathway. Based on the study results using doses of 30, 60, and 90 μM to enhance cell survival, the beneficial effects of AST were found to be dose-dependent, with the most pronounced effect observed at 90 μM [28].

Liu N. et al. stated in their research on brain aging that AST reduces neuronal death caused by oxidative stress from Aβ25-35 by activating the SIRT1/PGC-1α signaling pathway and also increases the expression of proteins associated with synapses and hippocampus pathways, specifically BDNF, SYN, SIRT1, and PGC-1α ($P < 0.05$). The study used a mouse model that was given an injection of Aβ 25–35, then given intragastric astaxanthin (0.1 ml/day, 10 mg/kg) for 30 consecutive days [29, 30].

Oxidative stress plays a significant role in various chronic diseases, including neurodegenerative disorders characterized by the formation of beta-amyloid (Aβ) plaques in brain tissue. *In vivo* studies have shown that Aβ25–35 can impair cognitive function, cause morphological changes in hip-

pocampal neurons, reduce Bcl-2 expression, and increase Bax expression. According to previous research, these proteins are involved in regulating cell death in neurons, granuloma cells, and Purkinje cells. Additionally, Aβ25–35 decreases superoxide dismutase and GSH-px levels while increasing reactive oxygen species and malondialdehyde levels [30].

Further *in vitro* studies indicate that Aβ25–35 can trigger oxidative stress, accelerate the aging process, and induce apoptosis in PC12 cells. Experiments using the Morris water maze revealed that injecting Aβ25–35 into the lateral ventricle of rats led to a decline in spatial memory and learning ability, which was associated with decreased expression of SYN and BDNF proteins in the hippocampus. BDNF is a crucial protein for central nervous system development and plays a role in neuron survival, differentiation, growth, and regeneration. Moreover, SYN functions as a marker of synaptic density and reflects synaptic transmission efficiency [29].

Astaxanthin has been proven to inhibit the production of ROS through the SIRT1/PGC-1α signaling pathway by enhancing antioxidant activity and exerting anti-aging effects in cells. Treatment with AST also suppresses aging and apoptosis in PC12 cells while increasing cellular resistance to ROS, indicating enhanced cellular activity. Through the SIRT1/PGC-1α pathway, AST can protect synaptic proteins, increase SYN and BDNF expression, and support improvements in learning ability, memory, and cognitive function, as reported by S. E. El-Agamy [31]. Furthermore, astaxanthin can cross the blood-brain barrier, so that it has the potential as a neuroprotective agent in the fight against neurodegenerative diseases. Astaxanthin has demonstrated promise in addressing neurodegenerative conditions such as Alzheimer's disease, Parkinson's disease, and cerebral ischemia, all of which involve oxidative stress as a key factor in their development [14].

A study conducted by X. Zhu et al. and Y. Nishida et al. in diabetic model mice showed that AST treatment improved renal morphological damage through increased total Nrf2 in the kidneys ($P < 0.05$) and also AST treatment significantly improved insulin resistance and glucose intolerance by increasing mitochondrial biogenesis in muscle tissue [32, 33]. This study used diabetic model mice given AST therapy (25 mg/kg i.g. daily) [32] and obese mice given AST therapy (1, 5, 25, or 50 μM) to improve skeletal muscle insulin resistance [33]. Diabetic nephropathy (DN) is the leading cause of end-stage renal disease associated with diabetes mellitus. Excessive ROS caused by hyperglycemia is involved in various signaling pathways, including protein kinase C (PKC), polyol, and hexosamine signaling, which contribute to diabetic complications. Additionally, ROS can stimulate the production of growth factors and cytokines, leading to renal cell hypertrophy or proliferation by increasing ECM expression and reducing its degradation, ultimately resulting in kidney fibrosis. In diabetes, the activity of antioxidant enzymes declines, weakening the ability to eliminate free radicals. Serum SOD activity reflects the capacity to scavenge oxygen free radicals, while MDA levels, as a final product of lipid peroxidation, indicate the severity of oxidative damage. This study demonstrates that AST enhances nuclear Nrf2 levels and upregulates HO-1 and SOD1 protein expression through Nrf2–ARE signaling activation, thereby reducing FN and Col IV accumulation, which helps delay the progression of DN. Moreover, AST improves the antioxidant capacity of diabetic rats and mitigates lipid peroxidation [32, 33].

Skeletal muscle plays a vital role in insulin-stimulated glucose uptake. Dysregulation of metabolic processes within skeletal muscle, particularly in the context of obesity, significantly contributes to the development of insulin resistance, a hallmark of type 2 diabetes. Insulin resistance in skeletal muscle is closely associated with mitochondrial dysfunction and oxidative stress, which are triggered by excess energy states and elevated levels of circulating free fatty acids (FFAs). To combat skeletal muscle insulin resistance and enhance energy expenditure, stimulating mitochondrial biogenesis is essential. This process helps maintain the mitochondrial pool, increases mitochondrial oxidative phosphorylation, and improves FFA metabolism. A study by Nishida et al. reported that both *in vivo* and *in vitro* experiments revealed that AST administration enhances AMPK activation in skeletal muscle and upregulates transcriptional coactivators and transcription factors, leading to mitochondrial remodeling [33]. This includes increased mitochondrial oxidative phosphorylation and FFA metabolism. Consequently, AST was identified as a potent exercise mimetic. AST treatment elevated the expression of Ppar-δ and Pdk4 in muscle, which stimulated mitochondrial gatekeeper proteins to promote mitochondrial biogenesis, while also improving running time and endurance, thereby further enhancing insulin resistance in HFD-fed mice. These effects are likely attributed to

AST's ability to stimulate mitochondrial biogenesis through the activation of the AMPK-PGC-1α pathway. Additionally, AST may offer protective effects through its strong antioxidant activity, particularly during high-intensity exercise when large amounts of ROS are generated. AST is also recognized as a powerful antioxidant against singlet oxygen and lipid peroxidation, helping to reduce oxidative muscle damage and associated inflammation [33].

Studies on cells conducted by Brasil et al. and Yang et al. [7, 34] administered chemical stressors to induce oxidative stress and mitochondrial dysfunction showed that AST functions as a strong mitochondrial protector by involving the PI3K/Akt/Nrf2/HO-1 signaling pathway in dopaminergic SH-SY5Y cells exposed to hydrogen peroxide ($H_2O_2$). This study utilized a rat spinal endplate chondrocyte model treated with various concentrations of AST (0, 5, 10, 20, 40, and 80 μM) and incubated for 24 or 48 h. Treatment with AST (20 μM) significantly reduced early apoptosis induced by oxidative stress, as well as late-stage apoptosis and necrosis in chondrocytes [34]. A study using the human neuroblastoma SH-SY5Y cell model, exposed to 300 μM $H_2O_2$ as a chemical stressor to induce redox imbalance and mitochondrial dysfunction, and treated with AST for 24 h prior to $H_2O_2$ exposure, showed that pretreatment with AST at concentrations of 10–40 μM significantly reduced the loss of SH-SY5Y cell viability induced by $H_2O_2$ [7].

The electron transport chain (ETC) continuously generates superoxide radical anions ($O_2^{-\bullet}$), which are then converted into $H_2O_2$ by the manganese-dependent superoxide dismutase (Mn-SOD) enzyme within the mitochondria [35]. As a non-radical species, $H_2O_2$ easily diffuses across cell membranes and acts as a signaling molecule. This compound can subsequently be converted into water through the action of CAT or GPx, either in the mitochondria or the cytoplasm, depending on the cell type. The reaction catalyzed by GPx requires glutathione (GSH), which can be synthesized by γ-glutamylcysteine ligase (γ-GCL) or recycled by glutathione reductase (GR) through a process that depends on the reduced form of NADPH [7]. Recent research has revealed that natural molecules can protect mitochondria through a mechanism dependent on Nrf2 activation [36]. In this study, scientists discovered that AST utilizes the PI3K/Akt/Nrf2/HO-1 signaling pathway to prevent mitochondrial dysfunction in SH-SY5Y cells exposed to $H_2O_2$. Pretreatment with AST reduced the impact of $H_2O_2$ on mitochondrial bioenergetics, including the activity of Krebs cycle enzymes, complexes I and V, as well as MMP and ATP levels. Additionally, AST played a role in maintaining redox balance by suppressing $O_2^{-\bullet}$ production by organelles and reducing lipid peroxidation, protein carbonylation, and nitration in mitochondrial membranes. Furthermore, AST prevented the activation of mitochondria-dependent cell death in cells exposed to $H_2O_2$ [7, 37].

A study conducted by G. Cui et al. aimed to explore how AST provides protection against heart damage caused by ochratoxin A (OTA) in rats [38]. This study used AST at a dose (100 mg/kg body weight, 0.1 ml per rat). The findings revealed that OTA exposure significantly reduced both body weight and heart weight in the test animals. Additionally, OTA led to a decrease in heart rate and lowered the levels of antioxidant enzymes such as SOD, CAT, and GSH in tissues, while increasing serum levels of cardiac enzymes (CK, CK-MB, and LDH) and tissue levels of MDA. Administration of ASX effectively improved heart rate, normalized cardiac enzyme levels, and elevated antioxidant levels. Histopathological analysis and TUNEL assay showed that ASX helped prevent myocardial injury induced by OTA. Western blot results also indicated that OTA upregulated the expression of Keap1, Bax, Caspase3, and Caspase9, while downregulating the expression of Nrf2, HO-1, and Bcl-2 proteins. The cardioprotective effect of ASX involves activation of the Keap1-Nrf2 signaling pathway and the mitochondrial-mediated apoptosis pathway. Nrf2 activation stimulates the production of antioxidant enzymes, detoxifying enzymes, and anti-inflammatory factors. Once released from Keap1, Nrf2 translocates into the nucleus, binds to the ARE element, and induces the expression of downstream antioxidant and detoxification genes, including SOD, CAT, NQO1, and HO-1. The study concludes that astaxanthin effectively protects against myocardial damage caused by OTA-induced oxidative stress and apoptosis [38].

*In vitro* studies on myoblasts, stem cells, liver cells, and neurons demonstrate that astaxanthin protects against cellular damage via the Nrf2 and PGC-1α pathways. Research on models of neurodegenerative, cardiovascular, liver, kidney, bone, and insulin resistance diseases indicate that astaxanthin, through the Nrf2 and PGC-1α pathways, can enhance cellular resistance to oxidative stress and mitigate mitochondrial dysfunction, which contributes to the pathogenesis of these diseases [7, 28, 34, 41, 42].

Astaxanthin enhances the expression of PGC-1α by activating specific signaling pathways, including AMPK (AMP-activated protein kinase) and SIRT1 (Sirtuin 1). The activation of AMPK and SIRT1 by astaxanthin promotes the transcription of PGC-1α, which is crucial for supporting mitochondrial biogenesis [40]. The Nrf2 and PGC-1α pathways work synergistically to regulate mitochondrial biogenesis [22, 27]. Nrf2 primarily focuses on protecting against oxidative stress and maintaining mitochondrial stability, while PGC-1α orchestrates the formation of new mitochondria through the activation of essential genes. The interplay between these two pathways is vital for sustaining cellular health and energy metabolism, particularly during periods of stress or high energy demand [16, 22].

*Conclusion*. Astaxanthin, a potent natural antioxidant, demonstrates significant potential in mitigating diseases related to oxidative stress and delaying the aging process. By modulating key cellular pathways such as Nrf2 and PGC-1, it not only combats oxidative damage but also enhances mitochondrial biogenesis, a critical process for maintaining cellular energy and function. Evidence suggests that astaxanthin may serve as a therapeutic agent for conditions associated with mitochondrial dysfunction, including neurodegenerative diseases, cardiovascular disorders, and metabolic syndromes. However, while preclinical and some clinical studies have highlighted these benefits, further research is essential to fully elucidate its molecular interactions, optimize dosage, and validate long-term safety and efficacy across diverse populations. Integrating astaxanthin into therapeutic strategies could represent a significant advancement in the treatment of oxidative stress-related pathologies and the promotion of healthy aging.

*Conflict of interest.* The authors have completed the Unified Conflicts of Interest form at http://ukrbiochemjournal.org/wp-content/uploads/2018/12/coi_disclosure.pdf and declare no conflict of interest.

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*Author contributions.* A.A.B conceived the study and drafted the initial manuscript. N.N.A.D and I.A.I.W reviewed, revised and approved the final version of the manuscript. All authors have read and agreed to the published version of the manuscript.

## АСТАКСАНТИН ЯК АНТИОКСИДАНТ: ДОСЛІДЖЕННЯ ЙОГО ПОТЕНЦІАЛУ У ПРОФІЛАКТИЦІ МІТОХОНДРІАЛЬНОЇ ДИСФУНКЦІЇ

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Астаксантин – природний каротиноїд, що має виражену антиоксидантну активність, високу стабільність і здатність долати як гематоенцефалічний, так і гемато-ретинальний бар'єри. Він проявляє високий потенціал у зменшенні наслідків захворювань, пов'язаних з окислювальним стресом. Мітохондрії є органелами, найбільш схильними до молекулярних пошкоджень, спричинених окислювальним стресом. Транскрипційні шляхи, які регулюються Nrf2 і PGC-1, відіграють вирішальну роль у підтримці функції та біогенезу мітохондрій. У даному огляді аналізується молекулярний механізм впливу астаксантину на шляхи Nrf2 і PGC-1α та здоров'я клітин.

Ключові слова: астаксантин, мітохондрії, окислювальний стрес, транскрипційні шляхи Nrf2 і PGC-1.

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