



The Effects of Astaxanthin on the Nervous System

Astaksantinin Sinir Sistemi Üzerindeki Etkileri

Ayris GÖKÇEOĞLU¹, Gül Fatma YARIM²

¹Ondokuz Mayıs University, Faculty of Veterinary Medicine, Department of Biochemistry, Samsun
• ayrisalt@gmail.com • ORCID > 0000-0002-2944-9122

²Ondokuz Mayıs University, Faculty of Veterinary Medicine, Department of Biochemistry, Samsun
• gulyarim@omu.edu.tr • ORCID > 0000-0003-4050-429X

Makale Bilgisi / Article Information

Makale Türü / Article Types: Derleme Makalesi / Review Article

Geliş Tarihi / Received: 29 Nisan / April 2022

Kabul Tarihi / Accepted: 24 Eylül / September 2022

Yıl / Year: 2022 | Cilt – Volume: 7 | Sayı – Issue: 3 | Sayfa / Pages: 657-674

Atıf/Cite as: Gökçeoğlu, A. and Yarım, G., F. "The Effects of Astaxanthin on the Nervous System" Journal of Samsun Health Sciences 7(3), December 2022: 657-674.

Sorumlu Yazar / Corresponding Author: Ayris GÖKÇEOĞLU

THE EFFECTS OF ASTAXANTHIN ON THE NERVOUS SYSTEM

ABSTRACT:

Astaxanthin is an antioxidant carotenoid abundant in the shells of crustaceans, salmon, trout, and other marine organisms. In both in vivo and in vitro experiments, astaxanthin has been proven to have a considerable impact on the neurological system. Astaxanthin exhibits these effects by modulating inflammation, suppressing oxidative stress, showing antioxidant effects, and suppressing neuronal apoptosis. In addition to its antioxidant, anti-inflammatory, and anti-apoptotic properties, astaxanthin has the potential to be used in the prophylaxis and treatment of neurological disorders due to its ability to cross the blood-brain barrier. Astaxanthin's commercial availability, lack of side effects, protective and therapeutic properties on the nervous system suggest that it may be a promising option in the future. In this review, information about the role of astaxanthin in the nervous system and its effects on neurological disorders are summarized.

Keywords: *Astaxanthin; Antioxidant; Neurological Disorders; Neuroprotective.*



ASTAKSANTİNİN SİNİR SİSTEMİ ÜZERİNDEKİ ETKİLERİ

ÖZ:

Astaksantin, kabuklular, somon, alabalık ve diğer deniz organizmalarının kabuklarında bol miktarda bulunan bir antioksidan karotenoiddir. Astaksantin nörolojik sistem üzerinde önemli etkiler gösterdiği gerek in vivo gerekse de in vitro çalışmalar sonucunda kanıtlanmıştır. Astaksantin anılan bu etkilerini, inflamasyonu modüle ederek, oksidatif stresi baskılayarak, antioksidan etki göstererek ve nöronal apoptozu baskılayarak sergilemektedir. Antioksidan, anti-inflamatuar ve anti-apoptotik niteliklerinin yanı sıra astaksantin kan-beyin bariyerini geçebilmesi nedeniyle nörolojik bozuklukların profilaksisinde ve tedavisinde kullanılma potansiyeline sahiptir. Astaksantin ticari olarak bulunabilirliği, yan etkisinin olmayışı, sinir sistemi üzerindeki koruyucu ve tedavi edici nitelikleri, gelecekte umut vadeden bir seçenek olabileceğini düşündürmektedir. Bu derlemede, astaksantin sinir sistemindeki rolü ve nörolojik bozukluklardaki etkileri hakkında bilgiler özetlenmiştir.

Anahtar Kelimeler: *Astaksantin; Antioksidan; Nörolojik Bozukluklar; Nöroprotektif.*

INTRODUCTION

Carotenoids are pigments found in plants, algae, bacteria, and fungi synthesized *de novo* (Higuera-Ciapara, et al., 2006). Lycopene is the source of carotenoids. The majority are 40-carbon hydrocarbons with two terminal rings linked by conjugated double bonds, also known as the polyene system (Urich, 1994; Adetunji et al., 2021). The carotenes, which are made up entirely of carbon and hydrogen, and the xanthophylls, which are oxygenated derivatives, have been identified as the most important. Oxygen can exist in the form of hydroxyl groups, oxo-groups, or a combination of both, as in astaxanthin (Higuera-Ciapara, et al., 2006).

Xanthophyll is a subclass of carotenoids that contain oxygen in their structure and are derived from lycopene (Wu et al., 2015). Astaxanthin is a red-orange oxycarotenoid pigment that is lipid-soluble and belongs to a group of xanthophylls (Baralic et al., 2015; Fakhri et al., 2018). Astaxanthin ($C_{40}H_{52}O_4$) has a 596.84 g/mol molar mass. It has a symmetrical structure and it is terminated by two rings linked by a polyene group (Wu et al., 2015). It has two asymmetric carbons at the 3, 3' locations of the β -ionone ring and hydroxyl groups (-OH) on both ends. When one hydroxyl group combines with a fatty acid, a mono-ester is formed, whereas when both hydroxyl groups react with fatty acids, a di-ester is formed. There are stereoisomers, geometric isomers, free and esterified forms of astaxanthin (Higuera-Ciapara, et al., 2006; Ambati et al., 2014). The chemical structure of astaxanthin was presented in Figure 1.

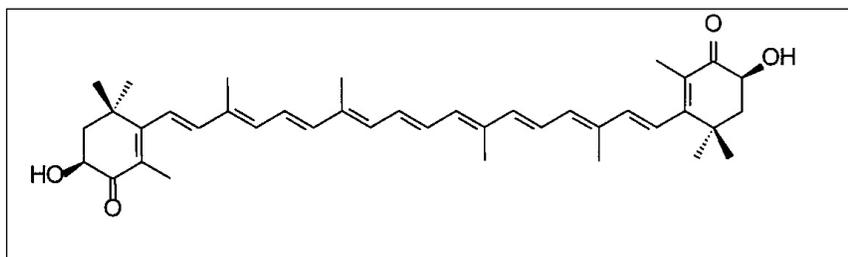


Fig. 1 Chemical structure of astaxanthin (Osterlie et al., 1999)

The super-antioxidant astaxanthin is known for its ability to reverse cellular damage caused by free radicals (Focsan et al., 2021). Astaxanthin's conjugated double bonds terminate free radical chain reactions by providing electrons and interacting with free radicals within the cell, giving this molecule powerful antioxidant qualities (Yuan et al., 2011; Zuluaga et al., 2018). Hydroxyl and carbonyl functional groups in ketocarotenoids such as astaxanthin make them excellent antioxidants (Seabra and Pedrosa, 2010). Astaxanthin is found in large amounts in the shells of crustaceans, salmon and trout, and other marine organisms and possesses significant biological effects (Chew et al., 2011).

The antioxidants, anti-inflammatory, and anti-apoptotic properties of astaxanthin contribute to its protective benefits (Lotfi et al., 2021). This molecule has also protected against primary brain damage, degeneration of neurons, blood-brain barrier (BBB) confusion, cerebral edema, and discomposed nerve function through anti-inflammatory effects in brain inflammation (Zhang et al., 2014).

THE ROLE OF ASTAXANTHIN IN NEUROLOGICAL DISORDERS

Astaxanthin is a dietary supplement that is available commercially, and it has no significant adverse effects. Astaxanthin can be measured in the brain tissue to pass across through the blood-brain barrier (Grimmig et al., 2017). Choi et al. (2008) have suggested that astaxanthin inhibited the synthesis of nitric oxide (NO), inducible nitric oxide synthase (iNOS), and cyclooxygenase-2 (COX-2) in lipopolysaccharide-stimulated BV-2 microglial cells. It showed that astaxanthin, through its antioxidant effects, suppressed COX-2 and iNOS activity and restricted the inflammatory mediators. Astaxanthin restrains traumatic brain injury by healing brain edema (Zhang et al., 2016).

The effects of astaxanthin on the prevention of multiple sclerosis were investigated in a chronic model of experimental autoimmune encephalomyelitis. Immunohistochemical examinations of the spinal cord and brain revealed that the inflammatory cell infiltration was restricted to the central nervous system. Astaxanthin's protective properties were also demonstrated by clinical behavior and illness severity (Bidaran et al., 2018).

Astaxanthin improves psychomotor and processing speed and has an ameliorative effect on cognitive functioning and it's reduces oligodendrocyte damage and myelin sheath disintegration in a rat multiple sclerosis (MS) model while decreasing demyelination and oligodendrocyte death (Ito et al., 2018; Lotfi et al., 2021). This molecule protects myelinated white matter and the number of motor neurons by neuronal apoptosis, diminishes pathological tissue damage, and improves functional recovery after spinal cord injury (Masoudi et al., 2017). It has been reported that the neuroprotective effect of astaxanthin in the central nervous system against 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine induced neurodegeneration was associated with diminished microglial activation as indicated by reduced immunohistochemical detection of ionized calcium-binding adaptor molecule 1 in the substantia nigra and striatum (Grimmig et al., 2017). *In vitro* research on the oxidative stress generated by lipopolysaccharides in C6 glial cells, astaxanthin revealed antioxidant capabilities. In male Sprague Dawley rats, astaxanthin exhibits therapeutic effects in chronic neuropathic pain (Sharma et al., 2018). Astaxanthin reduces reactive oxygen species (ROS) generation thus, it shows antiepileptic and

anti-inflammatory effects (Abdulqader, et al., 2021). The anti-oxidative properties of astaxanthin in neurological diseases was presented in Figure 2.

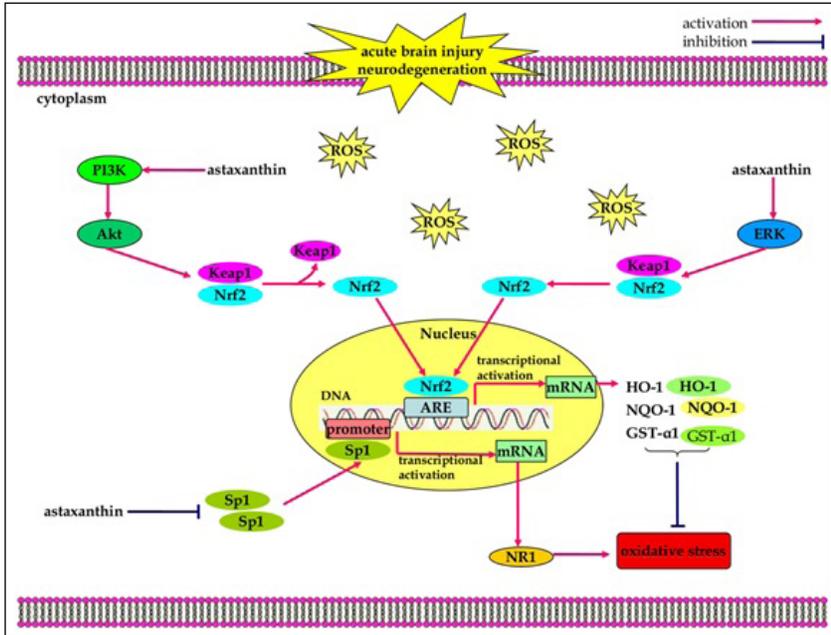


Fig. 2 The anti-oxidative properties of astaxanthin in neurological diseases (Wu et al., 2015).

The use of astaxanthin increased sensorimotor performance and improved cognitive function. Furthermore, therapy with astaxanthin reduced the amount of the damage and neuronal death in the brain cortex. In the cerebral cortex, astaxanthin restored the levels of brain-derived neurotrophic factor, growth-associated protein-43, synapsin, and synaptophysin, indicating that it promotes neuronal survival and plasticity (Ji et al., 2017). Pretreatment with astaxanthin protected the brain against transient ischemia-induced damage by lowering cerebral infarction volume, a finding that was linked to enhanced neurological performance following ischemia initiation. Ischemia-induced oxidative stress was reduced in rats pretreated with high amounts of astaxanthin. Astaxanthin reduced the size of the cerebral infarction and improved neurological function by inhibiting the formation of oxidative stress, activating the nuclear factor erythroid 2-related factor 2 antioxidant responsive element (Nrf2-ARE) neuroprotective pathway, increasing nerve cell regeneration and preventing cell death (Pan et al., 2017). Pretreatment with astaxanthin improves neurological function by lowering the edema in the brain,

the area of cerebral infarction, cerebral damage, and brain cell death. Furthermore, astaxanthin decreased the level of inflammatory mediators and increased the expression of nuclear anti-inflammatory mediators. Astaxanthin may protect against acute cerebral infarction, and the mechanism is thought to involve stimulating Nrf-2/HO-1 signaling to decrease oxidative stress, inflammation, and apoptosis (Yang et al., 2021).

The neuronal damage was significantly reduced after treatment with astaxanthin. Furthermore, astaxanthin significantly reduced ROS and malondialdehyde levels while increasing glutathione levels. Moreover, astaxanthin inhibited cytochrome c secretion and caspase-3 activity in the hippocampus. These findings imply that astaxanthin protects the rat hippocampus from neuronal loss caused by epilepsy by reducing lipid peroxidation, oxidative stress and blocking the mitochondrial apoptosis (Lu et al., 2015). In brain injury caused by ischemia-reperfusion, pretreatment with astaxanthin has been suggested to have a noticeable neuroprotective impact and antioxidant activity (Lu et al., 2010). The neuroprotective effects of astaxanthin was presented in Figure 3.

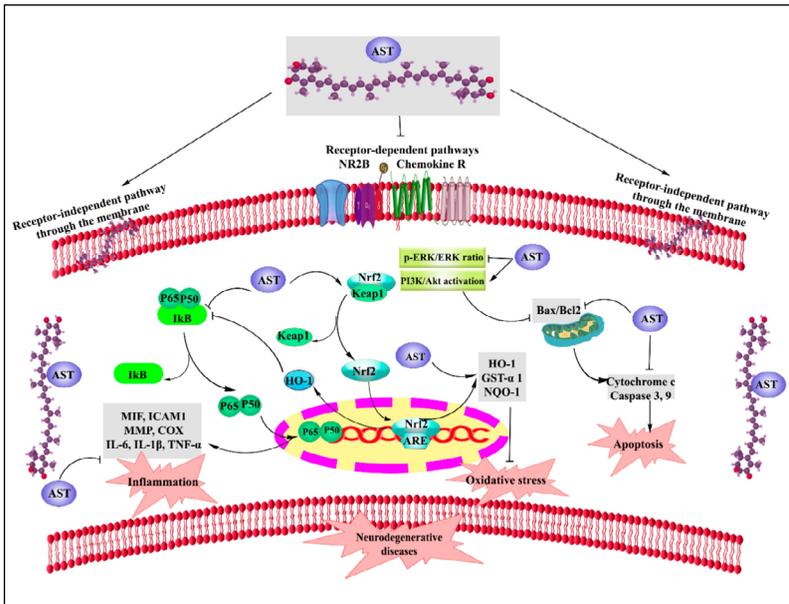


Fig. 3 Neuroprotective mechanisms of asthaxantin. AST: astaxanthin (Fakhri et al., 2019).

Zhou et al. (2021) have reported that down-regulating miR-31-5p by astaxanthin could be a possible therapeutic strategy for suppressing neuroinflammation by controlling microglia M1 activation. Astaxanthin could be a potential therapeutic for Alzheimer's disease through elevating low-density lipoprotein (LDL) receptor-related protein 1 expression, thus enhancing insulin sensitivity, autophagy induction and improving A β degradation (Babalola et al., 2021). The cerebral cortex had a higher concentration of astaxanthin than the rest of the brain. The cerebral cortex controls higher brain processes such as perception, voluntary movement, cognition, reasoning, memory, and psychomotor function (Manabe et al., 2018). The neuroinflammation that results from the use of kaliotoxin, a K⁺ channel blocker, is characterized by a neurodegenerative process. This model could be beneficial for researching neuronal degeneration and better understanding the underlying mechanisms in neurodegenerative disorders. The administration of astaxanthin restored inflammatory indicators and brain changes (Sifi et al., 2016).

CONCLUSION

Astaxanthin has been shown to significantly impact the nervous system in both *in vivo* and *in vitro* studies. It decreases pro-inflammatory cytokine levels lipid peroxidation, and oxidative stress, and blocks mitochondrial apoptosis. Astaxanthin increases anti-inflammatory cytokine levels. Furthermore, astaxanthin may be a potential therapeutic agent for neuroinflammation by reducing microglia activation. The use of astaxanthin improves sensory-motor performance and cognitive function. The effects of astaxanthin, which can cross the blood-brain barrier and is commercially available, are becoming increasingly relevant in neurodegenerative diseases. Considering the findings of scientific studies based on the administration of astaxanthin for its neuroprotective properties, it is clear that astaxanthin is a potential candidate for the prevention and/or treatment of neurodegenerative diseases in both humans and animals.

Conflict of Interest

No conflict of interest was declared by the authors.

Author Contribution

Design of Study: AG (%100)

Writing Up: AG (%50), GFY (%50)

Submission and Revision: AG (%50), GFY (%50)

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