Biological and neurological activities of astaxanthin (Review)

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Received April 18, 2022; Accepted June 30, 2022

DOI: 10.3892/mmr.2022.12816

Abstract. Astaxanthin is a lipid-soluble carotenoid produced by various microorganisms and marine animals, including bacteria, yeast, fungi, microalgae, shrimps and lobsters. Astaxanthin has antioxidant, anti-inflammatory and anti-apoptotic properties. These characteristics suggest that astaxanthin has health benefits and protects against various diseases. Owing to its ability to cross the blood-brain barrier, astaxanthin has received attention for its protective effects against neurological disorders, including Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, cerebral ischemia/reperfusion, subarachnoid hemorrhage, traumatic brain injury, spinal cord injury, cognitive impairment and neuropathic pain. Previous studies on the neurological effects of astaxanthin are mostly based on animal models and cellular experiments. Thus, the biological effects of astaxanthin on humans and its underlying mechanisms are still not fully understood. The present review summarizes the neuroprotective effects of astaxanthin, explores its mechanisms of action and draws attention to its potential clinical implications as a therapeutic agent.

Contents

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Abbreviations: AD, Alzheimer's disease; Akt, protein kinase B; ALS, amyotrophic lateral sclerosis; AST, astaxanthin; Aβ, amyloid-β peptide; BBB, blood-brain barrier; BDNF, brain-derived neurotrophic factor; CNS, central nervous system; Cyt c, cytochrome c; DDC, diethyldithiocarbamate; ERK, extracellular signal-regulated protein kinase; GAP-43, growth-associated protein 43; GFAP, glial fibrillary acidic protein; GSK-3β, glycogen synthase kinase 3β; HD, Huntington's disease; IKK, IκB kinase; iNOS, inducible nitric oxide; IR, ischemia/reperfusion; IS, ischemic stroke; LPO, lipid peroxidation; MAP-2, microtubule associated protein 2; MAPK, mitogen-activated protein kinase; MDA, malondialdehyde; MPP, 1-methyl-4-phenylpyridinium; NMDA, N-methyl-D-aspartate; NQO-1, NAD(P)H quinone oxidoreductase-1; NR1, NMDA receptor subunit 1; Nrf2, nuclear factor erythroid 2-related factor 2; OS, oxidative stress; PARP, poly (ADP-ribose) polymerase; PD, Parkinson's disease; PI3K, phosphoinositide 3-kinase; ROS, reactive oxygen species; SAH, subarachnoid hemorrhage; SOD, superoxide dismutase

Key words: astaxanthin, Alzheimer's disease, Parkinson disease, amyotrophic lateral sclerosis, cerebral ischemia/reperfusion, subarachnoid hemorrhage

1. Introduction

Astaxanthin (AST) is a lipid-soluble, red-orange pigment (1) that belongs to a group of carotenoids called xanthophylls, which includes β-cryptoxanthin, canthaxanthin, lutein and zeaxanthin (Fig. 1) (2). Since the antioxidant, anti-inflammatory and anti-apoptotic properties of AST have been demonstrated in several studies, leading to its approval as a dietary supplement (3).

AST has a molecular structure similar to those of β-carotene and other carotenoids (4). However, the oxygen groups in its molecular structure distinguish AST from other carotenoid subtypes (5). AST has a polar region at each end of the molecule's ionone rings that neutralizes free radicals. In contrast to the 11 carbon-carbon double polyunsaturated bonds in β-carotene, the central nonpolar zone of AST is made up of 13 bonds, which allow AST to remove high-energy electrons (6). The hydroxyl and ketone moieties on both rings increase the polarity of AST and greatly enhance its capacity to cross the cell membrane (7,8). These unique chemical properties bestow AST with some bioactivity-related advantages, including a higher antioxidant effect than other carotenoids (9). Owing to its carbon-carbon double polyunsaturated bonds, AST has two isomeric forms; trans and cis (Fig. 2A) (10). The cis isomer, cis-AST, includes 9-cis and 13-cis configurations (Fig. 2B). Due to the two stereogenic carbon atoms at the C-3 and C-3' positions, all-trans-AST has three stereoisomers: (3S, 3'S), (3R, 3'R) and (3R, 3'S) (Fig. 2C). The structure of all-trans-AST is more stable than that of cis-AST, indicating that all-trans-AST

is the predominant form of AST in nature (11). In addition, 3S, 3-S-AST is a more powerful antioxidant than the other stereoisomers (12). Owing to the stability of all-trans-AST, it has been used as an experimental material in several studies. Therefore, the aim of the present review was to explore the biological activities and neurological functions of all-trans-AST.

AST is extracted from microorganisms; phytoplankton; bacteria; yeast; and marine animals, such as shrimps, lobster, asteroidean, algae, crustaceans, trout, krill, red sea bream and salmon (13,14). In nature, AST is initially synthesized by microalgae and phytoplankton, accumulating in zooplankton and crustaceans and reaching higher level marine animals through the food chain (14). *Haematococcus pluvialis* (*H. pluvialis*) produces the largest quantity of natural AST (15). However, large-scale cultivation of *H. pluvialis* is considered costly (16); thus, synthetic production is currently the predominant source of AST. However, synthetic AST shows only 50% of the biological activity of natural AST (17).

Previous studies have shown that AST can mediate the processes of various diseases through antioxidant, anti-inflammatory and anti-apoptotic activities (Fig. 3). In a study of a diabetic retinopathy model, AST treatment increased the levels of the antioxidant enzyme heme oxygenase-1 (HO-1) and maintained the homeostasis of retinal ganglion cells (18). Yoshihisa *et al* (19) found that AST can protect keratinocytes from ultraviolet-related damage by decreasing the expression of oxidative factors [inducible nitric oxide, (iNOS)] and the inflammatory factors IL-1β and TNF-α. In addition, a clinical trial demonstrated that oral AST protects the skin from ultraviolet injury (20). Furthermore, AST maintains the homeostasis of lipid metabolism (21) and controls the courses of cardiovascular diseases and cancer by regulating apoptosis factors and cell proliferation (22,23).

Previous studies have identified the health benefits of AST against neurological disorders, including Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), amyotrophic lateral sclerosis (ALS), cerebral ischemia/reperfusion (IR), subarachnoid hemorrhage (SAH) and cognitive disorders (24,25). Therefore, the present review focused on the biological activities and neurological functions of AST.

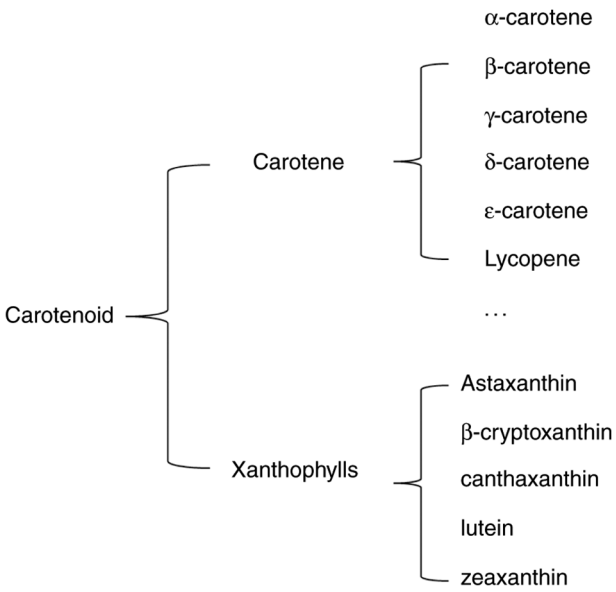

Figure 1. Classification of carotenoids.

2. Biological activities

Antioxidant activities of astaxanthin. Molecular oxygen (O_2) is the most significant radical in living systems. O_2 is a reactive oxygen species (ROS) that is generated through a series of metabolic and physical processes. Overproduction of ROS can result in oxidative stress (OS) (26). ROS and OS can have deleterious effects on the structures of cells, including lipids, membranes, proteins and DNA (27). Due to its unique features, AST can maintain the integrity of the cell membrane and mediate immune system function and gene expression by neutralizing O_2, scavenging radicals and managing lipid peroxidation (LPO) (28,29). In addition, some studies have indicated that the antioxidant activity of AST is more powerful than that of other carotenoids (30). Nakajima *et al* (31) found that AST exerts neuroprotective functions in a N-methyl-D-aspartate (NMDA)-induced excitotoxicity model by decreasing LPO and oxidative DNA damage. Another study shows that AST antagonizes OS in a 1-methyl-4-phenylpyridinium (MPP+)-induced PC12 cell model by decreasing the expression of NMDA receptor subunit 1 (NR1), which has previously been linked to neurodegenerative disorders (32).

AST activates the phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt) pathway (33) and the mitogen-activated protein kinase (MAPK)/extracellular signal-regulated protein kinase (ERK) pathway. The two pathways facilitate the dissociation of nuclear factor erythroid 2-related factor 2 (Nrf2) from Kelch-like ECH-associated protein 1. Nrf2 is translocated to the nucleus and activates the Nrf2 antioxidant response element (ARE) signaling pathway (33). The PI3K/Akt pathway upregulates the expression of HO-1, NAD(P)H quinone oxidoreductase-1 (NQO-1), glutathione-S-transferase-α1, the glutamate-cysteine ligase modifier subunit and the glutamate-cysteine ligase catalytic subunit, which provide protection against OS both *in vitro* and *in vivo* (24,34-36). In addition, it has been reported that rats fed AST show elevated levels of other antioxidant enzymes, such as superoxide dismutase (SOD), catalase (CAT) (37,38), thiobarbituric acid reactive substances and peroxidase, in the liver and plasma (24,39).

Anti-inflammatory activities of astaxanthin. Inflammation is a complex host defense response to infection, injury, ischemia, toxins and radiation. Inflammation also facilitates the tissue repair process through the actions of immune cells and inflammatory mediators. However, excessive or inappropriate inflammatory activity is deleterious to the host and can cause or aggravate numerous diseases (40). The NF-κB signaling pathway is an important and ubiquitous nuclear transcription pathway that serves important roles in inflammatory and immune responses (41). Excessive activation of the NF-κB signaling pathway is related to inflammatory changes in rheumatoid arthritis and heart and brain diseases. In unstimulated conditions, NF-κB (p50-p65) remains inactive in the cytoplasm and interacts with the inhibitory (IκB) family (IκB-α) (42). Under stimulation by extracellular agents, NF-κB is activated through dissociation of IκB, which is phosphorylated by

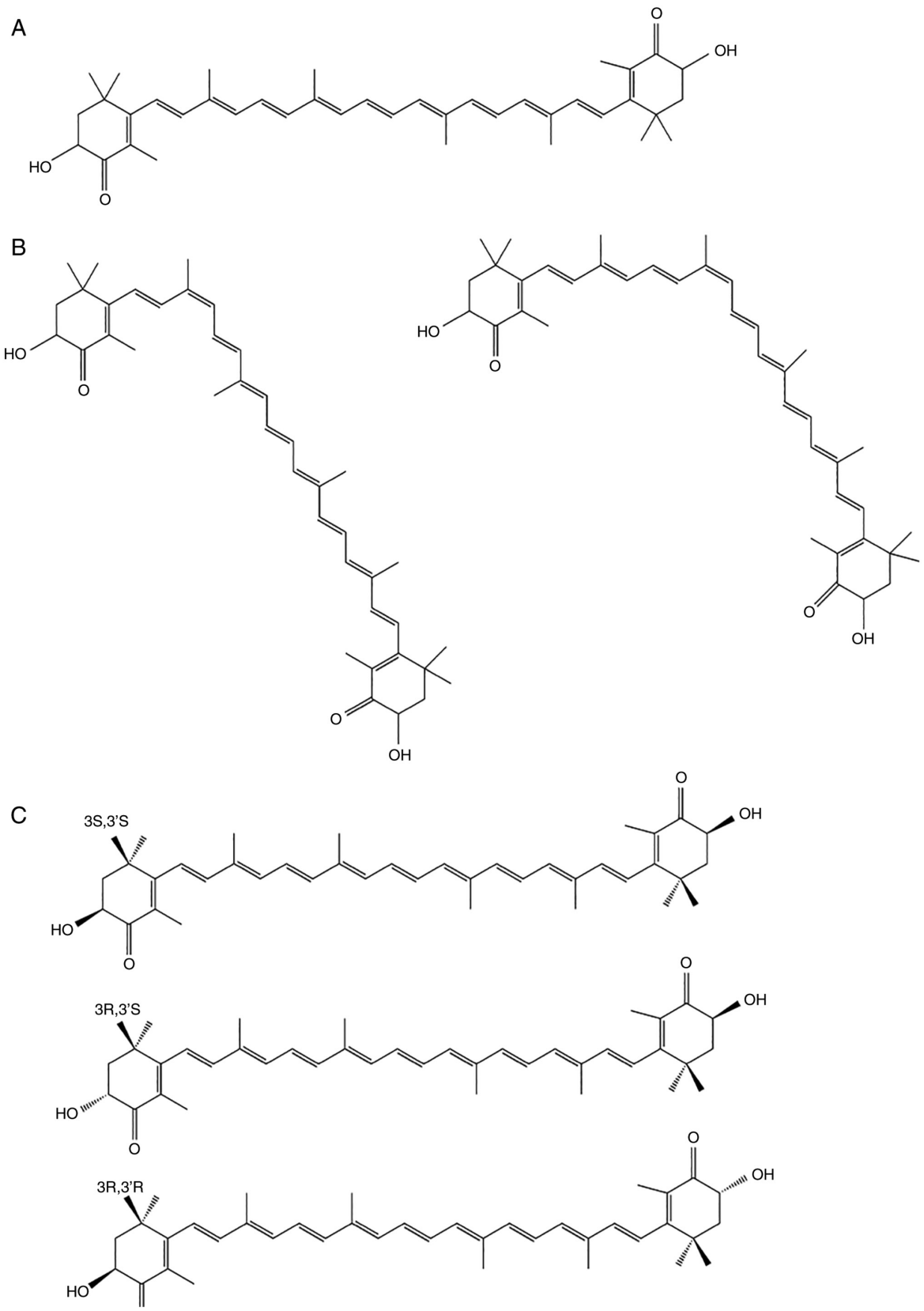

Figure 2. Structures of all-trans-astaxanthin (A), 9-cisastaxanthin, 13-cisastaxanthin (B) and (3S, 3'S), (3R, 3'R) and (3R, 3'S) all-trans-astaxanthin subtypes (C).

the IκB kinase complex (IKK, including IKKα and IKKβ). Dissociated NF-κB enters the nucleus and binds to κB regulatory elements that produce the pro-inflammatory cytokines IL-1β, IL-6 and TNF-α (41,43). Therefore, blocking the NF-κB signaling pathway is important for the mediation of inflammatory diseases. A recent study showed that AST can block excessive NF-κB signaling by downregulating the phosphorylation of IκB-α or increasing the cellular expression of IκB-α

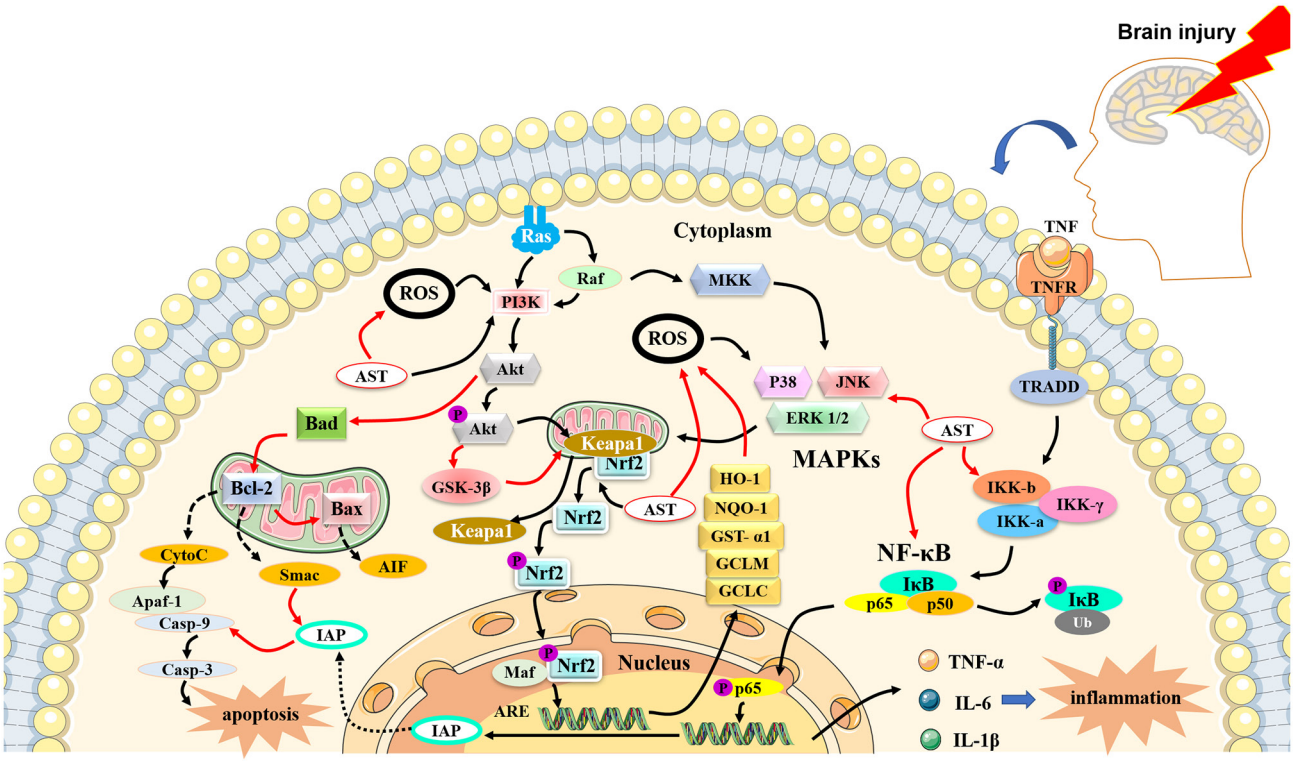

Figure 3. The antioxidant, anti-inflammatory and anti-apoptotic properties of AST. AST can activate phosphoinositide 3-kinase/protein kinase B and nuclear factor erythroid 2-related factor 2 signaling pathways, leading to the production of heme oxygenase-1, NAD(P)H quinone oxidoreductase-1, glutathione-S-transferase-α1, glutamate-cysteine ligase modifier subunit and glutamate-cysteine ligase catalytic subunit for the attenuation of oxidant effects. The NF-κB signaling pathway is initially activated by tumor necrosis factor and produces pro-inflammatory cytokines, chemokines and growth factors, such as IL-1β, IL-6 and tumor necrosis factor α. AST can block excessive NF-κB signaling and downregulate the expression of pro-inflammatory cytokines. AST reduces the expression of inflammatory factors and suppresses the activation of caspases and Bax, while increasing the level of Bcl-2. Red arrows indicate inhibitory action and black arrows denote enhancement action. AST, astaxanthin; Casp, caspase; MDA, malondialdehyde; IL-1β, interleukin-1 β; TNF-α, tumor necrosis factor α; IL-6, interleukin-6; JNK, c-Jun N-terminal kinase; AD, Alzheimer's disease; p-IKKα, p-IκB kinase α; Bcl-2, B-cell lymphoma-2; HO-1, heme oxygenase-1; Nrf2, nuclear factor erythroid 2-related factor 2; Akt, Akt, protein kinase B; GSK-3β, glycogen synthase kinase 3β; PARP, poly (ADP-ribose) polymerase; AIF, apoptosis inducing factor; ROS, reactive oxygen species; Bax, BCL2-Associated X; Cyt-c, cytochrome c; NMDA, N-methyl-D-aspartate; PD, Parkinson's disease; NOX2, nitrogen oxide 2; SOD, superoxide dismutase; GSH, glutathione; IR, ischemic reperfusion; NQO1, NAD(P)H quinone oxidoreductase-1; GFAP, glial fibrillary acidic protein;MAP-2, microtubule-associated protein-2; BDNF, brain-derived neurotrophic factor; GAP-43, growth-associated protein 43; NO, nitric oxide; iNOS, inducible nitric oxide; MDA, malondialdehyde; CAT, catalase; GPX, Glutathione peroxidase; GST-α1, glutathione-s-transferase-α1;SAH, subarachnoid hemorrhage; ICAM-1a, intercellular cell adhesion molecule-1 a; Apaf-1, apoptotic protease activating factor-1.

mRNA and protein (44). AST also exhibits anti-inflammatory effects by inhibiting cyclooxygenase-1 and nitric oxide in lipopolysaccharide-stimulated BV2 microglial cell biogenesis through the regulation of multiple genes (39).

Anti-apoptotic activities of astaxanthin. Apoptosis, a process of cell suicide, is a common mechanism in living systems. This process is vital for tissue development, maintenance of homeostasis and defense against a variety of extracellular and intracellular insults and mutations (45). However, excessive apoptosis disrupts homeostasis and leads to numerous diseases. The apoptotic pathway is regulated by the Bcl-2 family, including the pro-apoptotic cytokines Bad and Bax and the anti-apoptotic cytokines Bcl-2 and Bcl-xL (46,47). Under apoptotic stimulation, Bad and Bax promote the release of cytochrome c (Cyt c) from the mitochondria into the cytoplasm. A complex comprising Cyt c, apoptotic protease activator-1 and caspase-9 then activates caspase-3, which triggers apoptosis. Bcl-2 and Bcl-xL inhibit the release of Cyt c and induce apoptosis (48). In addition, the PI3K/Akt pathway inhibits Bad and Bax and the JAK/STAT pathway or the SCR/STAT pathway promotes the expression of Bcl-2 and Bcl-xL, contributing to anti-apoptosis.

AST can regulate some key apoptotic proteins and prevent related diseases (49). In addition, studies have shown that AST serves an important role in the activation of the PI3K/Akt signaling pathway, mediation of the phosphorylation of Bad and downregulation of the activation of Cyt c and caspase-3 (24,50-52). Fan *et al* (22) found that AST supplementation protects rats from homocysteine-related apoptosis through the regulation of Bcl-2 levels. In a study of a steatotic liver model, AST treatment reduced the expression of inflammatory factors and suppressed the activation of caspases and Bax while increasing the level of Bcl-2 (53).

3. Neuroprotective activities of astaxanthin

The central nervous system (CNS) is one of the most important systems in the human body and it contains billions of neuronal and glial cells. The blood-brain barrier (BBB) is a selectively permeable barrier between capillaries and the brain that isolates the CNS from other systems of the body. This barrier

is crucial for maintaining brain homeostasis and protecting the neuronal environment from harmful materials (54). However, the BBB occasionally prevents the transportation of therapeutic agents to the CNS for the treatment of neurological disorders. As mentioned previously, AST is a lipid-soluble pigment that can cross the BBB, a feature that is crucial for the treatment of neurological diseases. Manabe *et al* (55) found that AST accumulates in the hippocampi and cerebral cortexes of rat brains after single and repeated dietary ingestion. The accumulation of AST in the cerebral cortex may maintain and improve cognitive function. Some studies have shown that treatment using AST can promote nerve cell regeneration and increase gene expression of proteins important for brain recovery, such as glial fibrillary acidic protein (GFAP), microtubule associated protein 2 (MAP-2), brain-derived neurotrophic factor (BDNF) and growth-associated protein 43 (GAP-43) (56-59). GFAP serves significant roles in the repair of CNS injury, promotion of cell communication and alleviation of BBB damage (60). MAP-2 can regulate microtubule growth and neuronal regeneration. BDNF is responsible for neuronal survival and growth and the differentiation of new neurons (61), whereas upregulation of GAP-43 stimulates the protein kinase pathway and promotes neurite formation, regeneration and plasticity (61). The biological activities of AST in the courses of neurological diseases are summarized in Table I.

Protective activities of astaxanthin: AD. Neurodegenerative disorders are difficult to prevent and treat. In addition, improving their prognoses is quite challenging. AD is the most common neurodegenerative disorder among older individuals (62). Extensive research has demonstrated that the number of people with AD is steadily increasing. AD tends to have a long course, various comorbidities and medical requirements for long-term care. These data suggest that AD places a heavy socioeconomic burden on the families of patients and the society at large (63,64).

Patients with AD show a significant degree of oxidative damage in the brain. This oxidate damage is associated with the accumulation of amyloid-β peptide (Aβ) (65). Aβ is the main component of senile plaques, neurofibrillary tangles and neutrophil threads in the brain (66). In addition to Aβ, mitochondrial abnormalities and hyperphosphorylated tau also induce oxidative and inflammatory reactions that contribute to the pathology of AD (67). Furthermore, metal ions (68,69), LPO (66) and DNA abnormalities (70) are implicated in the oxidative process of AD.

AST, with its antioxidant and anti-inflammatory effects, is recommended for the prevention or reduction of the progression of AD and the improvement of its prognosis (37). Indeed, two double-blind placebo-controlled studies conducted in Japan demonstrate that AST supplementation could effectively improve cognitive ability, which enables individuals to accomplish tasks more precisely and rapidly (71,72). In their study, Taksima *et al* (73) found that Wistar rats treated with AST decreased their escape latency time and increased the time spent in the target quadrant in the Morris water maze test. AST intake has been found to reduce brain oxidative indices, such as the LPO product malondialdehyde (MDA) and the percentage of superoxide anion and increase glutathione peroxidase activity. A previous study demonstrated that neurodegenerative disorders may be related to insulin resistance, which could lead to the accumulation of Aβ, mitochondrial dysfunction and increased levels of inflammatory cytokines (74). In a previous animal study, Rahman *et al* (75) found that AST not only improved the cognitive assessment results of rats, but also attenuated central insulin resistance indicators, Aβ level and TNF-α level in the hippocampi of Wistar rats (76).

In a study of a PM2.5-induced neuroinflammation model, AST treatment decreased the expression of M1 pro-inflammatory cytokines (IL-1β, TNF-α and IL-6) and increased the expression of M2 anti-inflammatory cytokines (IL-10 and arginase-1) (77). Similar anti-inflammatory activities of AST have been reported in other studies. For example, a previous study showed that AST (50 μM) significantly reduces the release of inflammatory mediators in activated microglial cells through the modulation of factors involved in the NF-κB cascade (e.g., IKKα/β, IκBα, NF-κB p65, IL-6 and MAPK) (78). HT12 cells and PC12 cells are rat-derived neuronal cells that are used to imitate the nervous system *in vivo* for studying neurodegeneration. Another study demonstrated that after treatment using 1.25-5 μM AST, these neuronal cells are protected from neurotoxicity stimulated by glutamate-induced cytotoxicity and reduced lactate dehydrogenase (LDH) release. This protective effect is attributable to decreased caspase-3/8/9 expression, poly (ADP-ribose) polymerase (PARP), suppressed ROS accumulation, increased nuclear Nrf2 and HO-1 expression and modulated Akt/glycogen synthase kinase 3β (GSK-3β) signaling (79). It has been reported that AST improves the behavioral scores of rats in hippocampal-dependent tasks; however, the underlying molecular process is not fully understood. These results show that administration of AST can serve as an augmentative treatment for AD.

Protective activities of astaxanthin: PD. PD is the second most common neurodegenerative disease globally. As with AD, the proportion of the global population with PD is increasing (80). James Parkinson first described this disease as a 'shaking palsy' 200 years ago (81). It is now recognized as a complex and heterogeneous disorder characterized by classic motor symptoms (bradykinesia, rigidity and tremor) induced by the loss of dopaminergic neurons and non-motor manifestations (altered posture, balance and gait) (81). Numerous studies have shown that neuronal loss and formation of Lewy bodies are the pathological hallmarks of PD. These pathological features, which have been identified in the basal forebrain, anterior thalamus, hypothalamus, amygdala and cerebral cortex, disrupt the normal function of the brain and interrupt the actions of important chemical messengers, such as acetylcholine and dopamine (82). Although the pathogenesis of PD is not completely understood, increasing evidence from human and animal studies suggest that OS and mitochondrial and calcium dysfunction are important mediators in its pathogenesis (83). The antioxidant and anti-inflammatory properties of AST make it a promising therapeutic agent for PD. In a previous study of a PD model, AST was found to increase PC12 cell viability, decrease mRNA production and decrease the expression of proteins linked to neurodegenerative disorders, such as activated transcription factor Sp1 and

Table I. Biological effects of astaxanthin in Alzheimer's Disease, Parkinson Disease, Cerebral Ischemia/Reperfusion, Subarachnoid Hemorrhage and Amyotrophic lateral sclerosis.

Author, year	Target, cell line	Effect	Concentration	Intervention	Duration	Outcome	Disease	(Refs.)
Ito, 2019	Human	Neuroprotective	3 mg AST + 5 mg sesamin, oral	Post-treatment	12 weeks	Psychomotor speed,↑ processing speed	MCI	(71)
Sekikawa, 2020	Human	Neuroprotective	9 mg AST + 50 mg tocotrienol, oral	Post-treatment	12 weeks	Composite memory↑ and verbal memory	Cognition	(72)
Taksima, 2019	Male Wistar rats,	Anti-oxidant	10 mg/kg/day, oral	Post-treatment	30 days	Learning and memory↑ ability, glutathione peroxidase, neuronal survival; MDA, protein carbonyl	AD	(73)
Kim, 2020	BV-2 microglial cells	Anti-inflammatory	1-10 μg/ml	Pre-treatment	4 h	IL-1β, TNF-α,↑ IL-6, pJNK activation, neuronal cell death; IL-10 and ↓ arginase-1, Akt phosphorylation	AD	(77)
Kim, 2010	BV-2 microglial cells	Anti-inflammatory	25 μM	Pre-treatment	24 h	IL-6, p-IKKα,↓ p-IκBα, p-NF-κBp65	AD	(78) (79)
Wen, 2015	Hippocampal HT22 cells anti-oxidant,	Anti-apoptosis	1.25-5 μM	Pre-treatment	2 h	cell viability, Bcl-2, HO-1, Nrf2, p-Akt,p-GSK-3β (Ser9) caspase-3/8/9 activity,↓ PARP, AIF, ROS, Bax, Cyt-c		
Ye, 2013	PC12 cells	Anti-oxidant	10 μmol/l	Pre-treatment	2 h	PC12 cell viability;↑ activated transcription factor, NMDA receptor↓ subunit 1 protein and mRNA	PD	(32)
Ye, 2012	PC12 cells	Anti-oxidant	10 μM	Pre-treatment	2 h	ROS, NOX2↑ HO-1, Nrf2↓	PD	(84)
Brasil, 2021	Human neuroblastoma SH-SY5Y cells	Anti-oxidant	20 μM	Pre-treatment	24 h	H2O2-induced cytotoxicity↓ cytochrome c, caspase-9 and caspase-3, IL-1β and TNF-α; HO-1, Nrf2 ↑	PD	(85)

Table I. Continued.

Author, year	Target, cell line	Effect	Concentration	Intervention	Duration	Outcome	Disease	(Refs.)
Lee, 2011	Human neuroblastoma SH-SY5Y cells, C57BL/6 mice	Anti-oxidant	50 μM 10, 30 mg/kg/day/ (animal model)	Pre-treatment	24 h (cell), 28 days (animal model)	ROS, cytotoxicity,↓ a-synuclein Bax, caspase-3, argyrophilic neurons; Bcl-2, SOD,↑ catalase, tyrosine hydroxylase neurons	PD	(86)
Xue, 2017	Male mice	ICR anti-oxidant	10 mg/kg/day, intragastric	Post-treatment	28 days	Learning and memory↑ ability, GSH, SOD,Bcl-2; Cyt c, Bax↓	IR	(93)
Pan, 2017	Male (Sprague Dawley) rat	SD anti-oxidant	5 mg/kg, 10 mg/kg, intragastrical	Pre-treatment	7 days	Nrf2, HO-1, NQO1,↑ Bcl-2, GFAP, MAP-2, BDNF, GAP-43; Infarction volume, Bax↓	IR	(94)
Lee, 2010	Human SY5Y neuroblastoma cells male Wistar rats	SH-anti-oxidant	10, 25, 50, 100 μM 30 mg/kg, intra-peritoneally (animal model)	Pre-treatment	90 min (cells), 0 and 90 min of cerebral reperfusion (animal model)	Neuronal cell↑ density, HO-1; NO, iNOS↓	IR	(95)
Lu, 2010	Male Sprague-Dawley rats	Anti-oxidant	50, 80 mg/kg, oral	Pre-treatment	5 and 1 h before ischemia	Infarct volume↓ Cell viability↑	IR	(96)
Yang, 2021	SD rats	Anti-oxidant anti-inflammatory anti-apoptosis	100 mg/kg, gavage	Pre-treatment	3 days	brain edema,↓ cerebral infarct area, TNF-α; IL-1β, IL-6, MDA,↑ Bax Nrf-2, HO-1, Bcl-2, CAT, SOD, GPX	IR	(97)
Wu, 2014	Male SD rats	Anti-oxidant	0.1 mM, left ventricle injection	Post-treatment	24 h after SAH	Brain edema,↓ BBB disruption; neurological scores, Nrf2, HO-1, NQO1, ↑ GST-α1	SAH	(34)
Zhang, 2014	Male SD rats, male New Zealand rabbits	Anti-oxidant	0.01, 0.1 mmol/l intracerebroven-tricular injection 25, 75 mg/kg oral	Post-treatment	30 min after SAH, 3 h after SAH	Brain edema, caspase-3,↓ MDA; BBB permeability,↑ GSH, SOD	SAH	(103)

Table I. Continued.

Author, year	Target, cell line	Effect	Concentration	Intervention	Duration	Outcome	Disease	(Refs.)
Zhang, 2019	Male SD rats, C57BL/6 mice, TLR4 gene KO mice	Anti-inflammatory	01, 0.1 and 0.2 mM 20ml, left lateral ventricle injection (rat); 2.0 ml, right lateral ventricle injection (mice)	Post-treatment	30 min, 4 h, or 8 h after SAH (rats), 30 min after SAH (mice)	IL-1b,TNF-a,↓ ICAM-1a, CD68 (+) microglia, NF-κB p65, p-IκB, Toll-like receptor 4 activation; Cell viability↑	SAH	(102)
Wang, 2019	Male SD rats	Anti-apoptosis	75 mg/kg, gavage	Post-treatment	3 h after SAH	Mitochondrial↑ membrane potential, synaptic protein, nerve growth and neuronal differentiation factors; Bax/Bcl-2 ratio,↓ Cyt c, caspase-3	SAH	(104)
Isonaka, 2011	Wistar rats	Antioxidant	100 nM	Pretreatment	24 h pretreatment + 72 h treatment period	Neurite lengths↑	ALS	(109)

Up arrows denote enhancement action and down arrows indicate inhibitory action. AST, astaxanthin; MCI, mild cognitive impairment; MDA, malondialdehyde; IL-1β, interleukin-1 β; TNF-α, tumor necrosis factor α; IL-6, interleukin-6; JNK, c-Jun N-terminal kinase; AD, Alzheimer's disease; p-IKKα, p-IκB kinase α; Bcl-2, B-cell lymphoma-2; HO-1, heme oxygenase-1; Nrf2, nuclear factor erythroid 2-related factor 2; Akt, Akt, protein kinase B; GSK-3β, glycogen synthase kinase 3β; PARP, poly (ADP-ribose) polymerase; AIF, apoptosis inducing factor; ROS, reactive oxygen species; Bax, BCL2-Associated X; Cyt-c, cytochrome c; NMDA, N-methyl-D-aspartate; PD, Parkinson's disease; NOX2, nitrogen oxide 2; SOD, superoxide dismutase; GSH, glutathione; IR, ischemic reperfusion; NQO1, NAD(P)H quinone oxidoreductase-1; GFAP, glial fibrillary acidic protein;MAP-2, microtubule-associated protein-2; BDNF, brain-derived neurotrophic factor; GAP-43, growth-associated protein 43; NO, nitric oxide; iNOS, inducible nitric oxide; MDA, malondialdehyde; CAT, catalase; GPX, Glutathione peroxidase; BBB, blood-brain barrier; GST-α1, glutathione-s-transferase-α1;SAH, subarachnoid hemorrhage; ICAM-1a, intercellular cell adhesion molecule-1 a; ALS, amyotrophic lateral sclerosis.

NR1 (32). AST also suppresses NADPH oxidase 2 levels, generates ROS and considerably increases Nrf2 and HO-1 levels (84). Studies have demonstrated that AST induces mitochondrial protection and reduces oxidative injury through the ERK1/2 and PI3K/Akt/Nrf2/HO-1 pathways (36,85). In a study of MPP+/1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced apoptosis in SH-SY5Y cells and a PD model, Lee *et al* (86) found that AST shows anti-apoptotic and neuroprotective effects through the upregulation of Bcl-2 protein expression and the inhibition of Bax and α-synuclein expression and caspase-3 activation. However, there are currently no clinical trials on AST for the treatment of PD. Considering the findings of previous trials on PD and carotene (87), it is possible that AST could serve an important role in improving the progression of PD in the future.

Protective activities of astaxanthin: cerebral ischemia/reperfusion. Ischemic stroke (IS) has a high incidence rate and is one of the most common causes of serious morbidity and mortality worldwide (88). Blockage of cerebral blood flow results in pathophysiological responses, including excitotoxicity, mitochondrial disorders, ROS release, inflammatory changes, apoptosis, calcium imbalance and DNA damage (88,89). In a study of a rat model, IR was found to activate the redox-sensitive transcription factors NF-κB, AP-1, MAPKs, JNK and p38 under minimal activation of ERK (90). Superoxide dismutase (SOD) and glutathione (GSH), which are free radical scavengers found in the brain tissue after cerebral IR, can suppress the harmful effects of IS (91,92). Previous studies have shown the neuroprotective effect of AST in reducing adverse reactions related to cerebral IR injury during brain recovery (93-97).

Xue *et al* (93) investigated the potential neuroprotective effects of AST in a mouse model of vascular cognitive impairment induced by repeated IR injury. The results of the study demonstrated that AST improves learning and memory and ameliorates the loss of and ultrastructural changes in the hippocampal pyramidal neurons of mice with repeated IR injury. The strong antioxidant and anti-apoptotic effects of AST on hippocampal neurons may be attributed to the downregulation of MDA, Bax, Cyt c and cleaved caspase-3, as well as the upregulation of GSH, Bcl-2 and SOD.

Pan *et al* (94) found that administration of AST protects rats from cerebral ischemia damage induced by middle cerebral artery occlusion. These results demonstrate that pre-treatment with AST reduces cerebral infarction volume and cell death through upregulation of Bcl-2 and inhibition of Bax. Furthermore, AST increases the expression of Nrf2, HO-1 and NQO-1 through the ARE signaling pathway. It has been reported that expressions of GFAP, MAP-2, BDNF and GAP-43 are significantly upregulated in rats with high AST levels. Lee *et al* (95) also found that AST reduces the level of iNOS and increases the levels of HO-1 and heat shock protein 70 after oxygen glucose deprivation injury. Further research has shown that AST has protective and anti-apoptotic effects against IR injuries (96,97).

Protective activities of astaxanthin: subarachnoid hemorrhage and amyotrophic lateral sclerosis. SAH is a severe disease with high morbidity and mortality rates worldwide. The clinical symptoms of SAH include coma and varying degrees of neurological disorders, such as aphasia, hemiplegia, hemianopia, paresthesia, headache and dysphrenia (98). The pathological course of SAH within the first 72 h is defined as early brain injury, which includes destruction of the BBB, cerebral edema, inflammation, increased intracranial pressure and neuronal apoptosis (99-101). These changes suggest an unfavorable prognosis and create significant individual and social burden. A series of studies conducted by Zhang *et al* (102) showed that AST ameliorates inflammation and OS and improves neuronal survival in SAH by modifying the Nrf2-ARE and Akt/Bad pathways and the toll-like receptor 4 signaling pathway (34). As mentioned previously, these pathways can inhibit the expression of inflammatory cytokines (IL-1β, TNF-α and NF-κB p65) and apoptotic cytokines (Bax, Cyt c and caspase-3) while rescuing mitochondrial function and BBB integrity (34,52,102,103). Wang *et al* (104) show that AST inhibits mitochondria-associated neuronal apoptosis after SAH by stabilizing the mitochondrial membrane potential, decreasing the Bax/Bcl-2 ratio, inhibiting Cyt c and suppressing caspase-3 enzyme activity. In addition, AST has been found to restore the expression of synapsin-1, postsynaptic density-95, GAP-4, BDNF and purine-rich binding protein-α associated with nerve growth and neuronal differentiation.

ALS is a progressive and lethal neurological disease characterized by irreversible loss of the upper and lower spinal or bulbar motor neurons (105). Most patients with ALS experience muscle paralysis until death, which is caused by respiratory failure within 3-5 years of the onset of symptoms. The number of patients with ALS has been rapidly increasing as a result of increasing aging of the global population. It has been reported that approximately 400,000 people worldwide will have ALS by 2040 (106). Although the underlying mechanisms of ALS are not fully understood, the most common cause may be related to a mutation in the gene encoding Cu/Zn SOD1. SOD1 is a significant cytosolic metalloenzyme that catalyzes the dismutation of the superoxide anion radical (O_2^-) into H_2O_2 and O_2. In addition, mitochondrial dysfunction, neuroinflammation and calcium flux-related excitotoxicity serve important roles in the progression of ALS (105,107). The unstable structure of mutant SOD1 leads to the accumulation free radicals from OS. OS causes oxidative damage to lipids, proteins and nucleic acids, resulting in neuronal death. Free radicals can be produced by antioxidants, such as vitamin C, vitamin E and AST. Bond *et al* (108) showed that antioxidants are promising as therapeutic agents for increasing the quality of life of patients with ALS. Moreover, Isonaka *et al* (109) demonstrate that spinal motor neurons treated with antioxidants and the SOD1 inhibitor diethyldithiocarbamate (DDC) have longer neurite lengths than neurons treated with DDC alone, indicating that antioxidants may improve pathological changes in ALS. In addition, clinical dietary studies have shown that carotenoid intake improves respiratory function in patients with ALS and reduces the risk for the disease (110,111).

4. Conclusion

AST, with its antioxidant, anti-inflammatory and anti-apoptotic properties, has various health benefits for humans. The present review highlighted the mechanisms of action

and benefits of AST in neurological diseases. In addition, owing to its lipid-soluble characteristics, AST may serve an important role in improving neurological diseases. However, previous studies on AST are mainly focused on animal models. Thus, further *in vivo* and *in vitro* studies on AST are warranted to clarify the specific signaling pathways involved in its effects and to elucidate its benefits for effective therapy. More research is needed to explore the potential applications of AST in the prevention, management and treatment of neurological diseases.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

Data sharing is not applicable to this article, as no data sets were generated or analyzed during the current study.

Authors' contributions

PS was a major contributor to writing the manuscript and prepared the figures. CZ performed the literature search and selection and was responsible for editing the references. The two authors read and approved the final version of the manuscript, were responsible for all aspects of the work and approved the submission in its current form. Data authentication is not applicable.

Ethics approval and consent to participate

No applicable.

Patient consent for publication

No applicable.

Competing interests

The authors declare that they have no competing interests.

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