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A marine-derived antioxidant astaxanthin as a potential neuroprotective and neurotherapeutic agent: A review of its efficacy on neurodegenerative conditions

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ABSTRACT

Astaxanthin is a potent lipid-soluble carotenoid produced by several different freshwater and marine microorganisms, including microalgae, bacteria, fungi, and yeast. The proven therapeutic effects of astaxanthin against different diseases have made this carotenoid popular in the nutraceutical market and among consumers. Recently, astaxanthin is also receiving attention for its effects in the co-adjuvant treatment or prevention of neurological pathologies. In this systematic review, studies evaluating the efficacy of astaxanthin against different neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, multiple sclerosis, cerebrovascular diseases, and spinal cord injury are analyzed. Based on the current literature, astaxanthin shows potential biological activity in both *in vitro* and *in vivo* models. In addition, its preventive and therapeutic activities against the above-mentioned diseases have been emphasized in studies with different experimental designs. In contrast, none of the 59 studies reviewed reported any safety concerns or adverse health effects as a result of astaxanthin supplementation. The preventive or therapeutic role of astaxanthin may vary depending on the dosage and route of administration. Although there is a consensus in the literature regarding its effectiveness against the specified diseases, it is important to determine the safe intake levels of synthetic and natural forms and to determine the most effective forms for oral intake.

1. Introduction

Carotenoids, which have attracted scientific and commercial interest due to their chemical diversity and beneficial effects on human health, are a broad class of bio-pigments, typically yellow, orange, and red in color and found in plants, algae, bacteria, and fungi. The total number of carotenoids characterized since Kuhn and Karrer first discovered β-carotene in 1930 is approximately 750 (Galasso et al., 2017, 2018; Patil et al., 2022). Carotenoids, consisting of 40 carbon atoms mostly joined by double bonds, are generally divided into two groups: carotenes and xanthophylls. Carotenes consist of carbon and hydrogen atoms, while xanthophylls contain at least one of the hydroxy and keto groups in addition to carbon and hydrogen (Nair et al., 2023). Carotenoids have been shown to have health-promoting properties in humans. In addition to their immunomodulatory, antioxidant, anticarcinogenic, and anti-aging roles, they are known to be protective against chronic non-communicable diseases such as cardiovascular diseases, cancer, respiratory diseases, and diabetes (Galasso et al., 2018; Patil et al., 2022).

More than 250 of the carotenoids discovered to date originate from marine algae, marine plants, or marine bacteria (Galasso et al., 2017). Marine animals, on the other hand, can accumulate carotenoids directly by obtaining them from foods or partially convert them metabolically (Bahbah et al., 2021). They show structural variations, such as allenic and acetylenic carotenoids. Some of the currently known marine-origin carotenoids are lutein, zeaxanthin, fucoxanthin, fucoxanthinol, halocynthiaxanthin, tedaniaxanthin, alloxanthin, mytiloxanthin, saproxanthin, neoxanthin, violaxanthin, antheraxanthin, siphonaxanthin, dinoxanthin, diadinoxanthin, salinixanthin, canthaxanthin, and astaxanthin (Galasso et al., 2017). Marine carotenoids act in oxidation-related pathways with various mechanisms, such as converting metal derivatives into harmless molecules and hydroperoxides into

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stable compounds, quenching singlet molecular oxygen, and inhibiting the autoxidation chain reaction (Bahbah et al., 2021). Among these, astaxanthin, a marine ketocarotenoid that has recently begun attracting attention, stands out with its significant antioxidant properties (Ahirwar et al., 2022).

Astaxanthin (3,3′-dihydroxy-β,β-carotene-4,4′-dione) was first commercially used in animal feed due to its vibrant red color. It has been recognized as a functional ingredient since its superior biological activity was discovered in the 1990s (Cao et al., 2023). Today, the use of astaxanthin as a nutraceutical, food additive, pharmaceutical, and even cosmeceutical ingredient is globally widespread (Galasso et al., 2018; Liu et al., 2023b). In some countries it is also used to improve the quality of foods and beers (Stachowiak and Szulc, 2021). The primary sources from which astaxanthin is synthesized de novo are green microalgae (*Haematococcus pluvialis* and *Chlorella zofingiensis*), red yeast (*Xanthophyllomyces dendrorhous*, also known as *Phaffia rhodozyma*), marine bacteria (*Agrobacterium aurantiacum* and *Paracoccus carotinifaciens*), and some plants of the genus Adonis (*Adonis aestivalis*, *Adonis amurensis*, and *Adonis annua*) (Galasso et al., 2018; Patil et al., 2022). *Haematococcus pluvialis* as a microalgal species, *Xanthophyllomyces dendrorhous* as red yeast, and *Paracoccus carotinifaciens* as a marine bacterium are used in commercial astaxanthin production. The most preferred source for commercial products is *Haematococcus pluvialis* with 3.8–5.0% astaxanthin by dry weight (Cao et al., 2023; Patil et al., 2022). The most important marine animals that accumulate astaxanthin via the food chain are krill, rainbow trout, salmon, shrimp, lobster, and fish eggs. Therefore, these types of seafood are sources of natural astaxanthin in the human diet (Cao et al., 2023; Galasso et al., 2018).

The increasing interest in astaxanthin has encouraged researchers to study artificial products that mimic natural astaxanthin. As a result, the artificial synthesis of the 3S,3′S enantiomer of astaxanthin was achieved (Fassett and Coombes, 2009). More than 95% of the astaxanthin on the market is reported to be of synthetic form (Lee and Ding, 1994). Disodium disuccinate astaxanthin (DDA), a synthetic form of astaxanthin, has been used in experimental models of myocardial ischemia-reperfusion, while CDX-085, another synthetic form of astaxanthin, has been used to treat liver inflammatory diseases, reduce triglycerides, prevent re-thrombosis, and improve metabolic syndrome (Lockwood and Gross, 2005; Patil et al., 2022). However, the anti-inflammatory and antioxidant properties of synthetic astaxanthin are still inferior to those of algae-based natural astaxanthin (Capelli et al., 2013). Natural astaxanthin (3S,3′S) has sustained the focused attention of researchers, particularly because its antioxidant effects are about 20–50 times stronger than those of synthetic astaxanthin (Ahirwar et al., 2022). It is more than 90% esterified, whereas synthetic astaxanthin is in the free form or unesterified. Thanks to this property, natural astaxanthin can interact with fatty acids at both ends, which allows for high bioavailability (Capelli et al., 2013). Alongside these advantages of natural astaxanthin, it has been reported that synthetic astaxanthin may cause some local adverse effects in the human body (Stachowiak and Szulc, 2021). There are also health concerns about different stereochemical derivatives and synthesis intermediates of synthetic astaxanthin. Therefore, synthetic astaxanthin varieties are only approved for use as additives in aquaculture feeds (Shah et al., 2016).

The process of digesting and absorbing astaxanthin is similar to that for lipids and carotenoids. However, different dietary components affect the bioavailability of astaxanthin. Co-ingestion of astaxanthin with olive oil or fish oil has been shown to increase its antioxidant activity (Otton et al., 2012; Rao et al., 2010, 2013). In particular, co-ingestion with fish oil decreased nitric oxide (NO) production and increased the release of antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) (Otton et al., 2012). Diets high in cholesterol have also been shown to increase the absorption of astaxanthin (Barros et al., 2012). In order for astaxanthin to be transported to the liver via the lymphatic system, it must accumulate in lipid droplets after absorption. It is then incorporated into micelles in the small intestine where it encounters bile acids, phospholipids, and lipases. Micelles are transferred to enterocytes by passive diffusion (Grimmig et al., 2017b). The transport of astaxanthin in circulation and its uptake into tissues are mediated by lipoproteins (Olson, 1994). Astaxanthin extracted from *Haematococcus pluvialis* was recommended as "generally recognized as safe" (GRAS) by the United States Food and Drug Administration (US FDA) in 1999 (Lorenz and Cysewski, 2000). In addition, the European Food Safety Authority (EFSA) has reported that the safe level of astaxanthin intake in humans is 0.034 mg/kg and it can be used as a dietary supplement (Davinelli et al., 2018; Rodríguez-Sifuentes et al., 2021). However, it should be noted that no significant side effects have been reported with astaxanthin supplementation (Grimmig et al., 2017b). Even excessive doses were shown to have no adverse effects on fibrinolytic and coagulation functions (Serebruany et al., 2010). A single 40-mg dose of astaxanthin, which has a half-life of 16–21 h, has been reported to be well tolerated (Bahbah et al., 2021).

1.1. Structure of astaxanthin

The structure of astaxanthin was first proven by Cooper et al. (1975). It molecularly consists of a long nonpolar polyene chain of conjugated double bonds in the middle and polar β-ionone rings at both ends of that chain. The β-ionone rings contain hydroxyl (-OH) and ketone (-C═O) groups. The polyene chain acts as a chromophore due to the multiple conjugated double bonds it contains. The compound's bright red color is due to this. It has a polar-nonpolar-polar structure (Liu et al., 2023b). It is able to adhere to both sides of the bilayer cell membrane thanks to the hydrophilic groups on the lipophilic polyene chain and β-ionone rings. Astaxanthin's excellent antioxidant properties derive from the ability of this unique molecular structure to be positioned vertically in the bilayer cell membrane (Brotosudarmo et al., 2020). The positioning of one of the polar β-ionone rings in the inner cytoplasmic environment and the other in the outer aqueous environment ensures efficient electron transfer across the double bonds of the polyene chain and contributes to the scavenging of free radicals on and within the membrane surface (Kidd, 2011; Yu and Liu, 2020) (Fig. 1). Astaxanthin absorbs free radicals into the polyene chain, donates electrons, and forms chemical bonds with reactive oxygen and nitrogen species. This versatile antioxidant activity distinguishes astaxanthin from other carotenoids. Due to all these features, astaxanthin is considered a master in protecting the cell membrane (Grimmig et al., 2017b).

Astaxanthin structurally contains chiral carbon atoms as well as conjugated double bonds. These two chiral centers produce two enantiomers (3S,3′S and 3R,3′R) and a meso form (3R,3′S). In addition to these optical isomeric forms of astaxanthin, there are also E and Z geometric isomeric forms (trans and cis) (Lee et al., 2014). The majority of astaxanthin in nature originates from *Haematococcus pluvialis* and is optically 3S,3′S and geometrically of the all-E isomeric form (Zhekisheva et al., 2002). There are 271 Z isomers and 1 all-E isomer of astaxanthin. Natural isomers include "9-Z," "13-Z," "15-Z," "9,13-di-Z," and "9,15-di-Z," while unnatural isomers include "9,13,15-tri-Z" (Liu et al., 2023b). Since the stability of the Z isomers is weaker than that of the all-E isomer, the all-E isomer predominates in nature (Weesie et al., 1995). However, there is evidence that the Z isomer has more antioxidant, anti-inflammatory, and anti-aging potential than the all-E isomer (Alugoju et al., 2023; Liu et al., 2018; Yang et al., 2017, 2019).

Since free astaxanthin is prone to oxidation and aggregation, natural astaxanthin is predominantly found in forms esterified with fatty acids at one or both ends (Miao et al., 2013). It can conjugate with proteins or lipoproteins as well as fatty acids, ultimately forming carotenoproteins or carotenolipoproteins, which can be seen in blue/purple hues (Tahergorabi et al., 2021). Astaxanthin in the diesterified form is particularly advantageous in terms of health benefits and has high thermostability against different cooking methods such as boiling, frying, and microwaving (Yang et al., 2015). It has been reported that astaxanthin in edible oils can withstand temperatures between 70 °C and

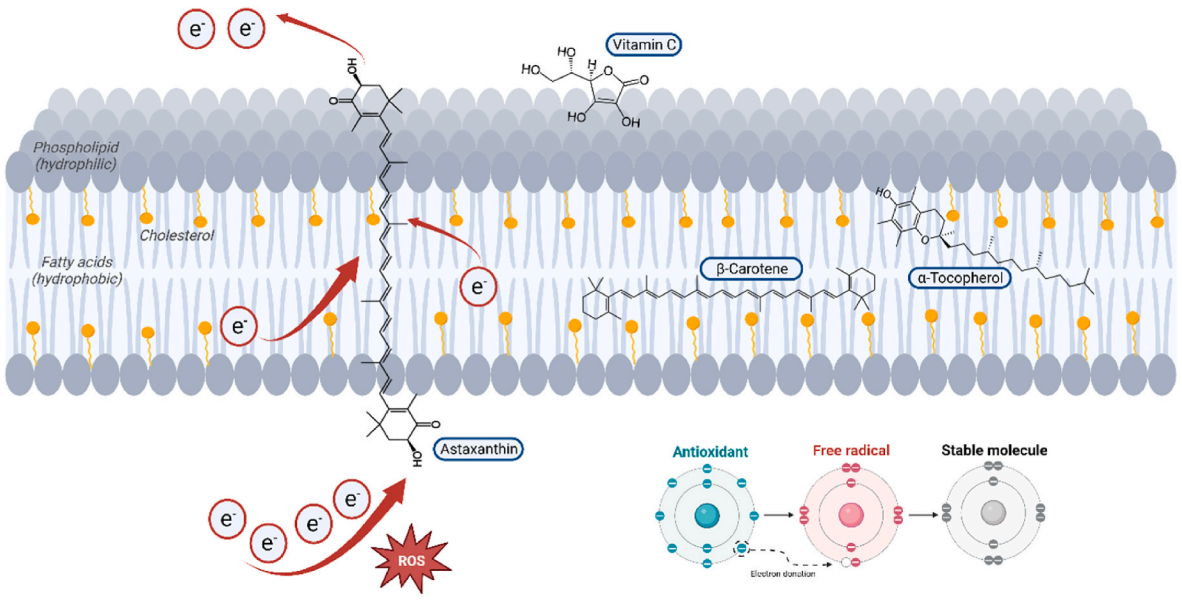

Fig. 1. The structure of astaxanthin and its vertical positioning in the bilayer cell membrane.

90 °C to a very high extent (90%) (Rao et al., 2007).

1.2. General health benefits of astaxanthin's molecular activities

Reactive oxygen species (ROS), among the by-products of cellular metabolism, are continuously produced in the living body. Over-exposure to oxidation triggers deoxyribonucleic acid (DNA), protein, and lipid damage, which can lead to various diseases. Carotenoids, the most widely known antioxidants, are active in protecting living tissues against oxidative damage. The polyene chain that forms the main skeleton of carotenoids quenches singlet oxygen and scavenges free radicals (Liu et al., 2023b). Astaxanthin is considered to be one of the most effective carotenoids as evidence shows its inhibitory role against oxidative stress and inflammation, dangerous processes that underlie many chronic diseases (Galasso et al., 2018). Astaxanthin has been reported to be approximately 10 times more potent as an antioxidant than β-carotene and lutein (Yuan et al., 2011) and approximately 500 times more potent than α-tocopherol (Aracati et al., 2022). Its antioxidation capacity has also been reported to be 560 times stronger than that of green tea catechins, 800 times stronger than coenzyme Q10, 3000 times stronger than resveratrol, and 6000 times stronger than vitamin C (Patil et al., 2022).

Evidence suggests that oxidative stress triggers chronic inflammation, which in turn underlies the pathophysiology of cancer, cardiovascular disease, diabetes, and neurological conditions (Khansari et al., 2009; Reuter et al., 2010). M1 macrophages produce various proinflammatory cytokines in response to increased ROS production. Clinical and experimental studies have shown that astaxanthin suppresses the production of cytokines such as interleukin (IL)-1β, IL-6 and tumor necrosis factor-α (TNF-α) (Park et al., 2010; Speranza et al., 2012). It also shows anti-inflammatory effects by inhibiting the cyclooxygenase-1 (COX-1) enzyme and nitric oxide (NO) (Choi et al., 2008; Park et al., 2018). Astaxanthin is a potential key regulator of transcription factors involved in antioxidant and anti-inflammatory mechanisms, such as Nuclear factor erythroid 2-related factor 2 (Nrf2) and nuclear factor kappa B (NF-κB) (Cao et al., 2023). Nrf2 is an important transcriptional regulator of hundreds of genes involved in dampening oxidative stress (Davinelli et al., 2014; Malhotra et al., 2010). In contrast, many genes that trigger inflammation and oxidative stress are regulated by NF-κB (Liu et al., 2017; Mercurio and Manning, 1999). Some of the important target genes of Nrf2 activation are nicotinamide adenine dinucleotide (phosphate) reduced:quinone oxidoreductase (NQO1), heme oxygenase 1 (HO-1), and glutathione-S-transferase (GST) (Joshi and Johnson, 2012). In addition, enzymes that induce superoxide and peroxide catabolism such as SOD, peroxiredoxin (Prx), and GPx are regulated by Nrf2 (Ma, 2013). On the other hand, NF-κB activation usually targets proinflammatory mediator genes (Liu et al., 2017). Studies have reported that astaxanthin activates Nrf2 and inhibits NF-κB, thereby reducing oxidative stress and inflammation (Bellezza et al., 2010; Kohandel et al., 2021; Wardyn et al., 2015). Other studies have reported that astaxanthin regulates HO-1, SOD, GPx, GST, and NQO1 in relation to the Nrf2 and NF-κB pathways in different tissues such as brain, kidney, liver, and alveolar epithelium (Guo et al., 2021; Ma et al., 2020; Song et al., 2014; Wu et al., 2014a) (Fig. 2).

Astaxanthin inhibits neutrophil recruitment associated with alcoholic hepatitis and cytokines induced during ethanol metabolism by in combination with signal transducer and activator of transcription 3 (STAT3), which downregulates genes related to antioxidation and anti-inflammation (Han et al., 2019). The downregulation of different pathways associated with lung injury by astaxanthin has been reported to attenuate the disease (Cheng and Eroglu, 2021). In a different study, astaxanthin was found to protect against isoprenaline-induced myocardial infarction by significantly restricting toll-like receptor-4 (TLR4), which mediates the production of proinflammatory cytokines (Zaafan and Abdelhamid, 2021). Astaxanthin also reduced keratinocyte apoptosis by inhibiting NO and prostaglandin E2 production in ultraviolet-induced skin inflammation (Yoshihisa et al., 2014).

Astaxanthin has lipid-lowering and anti-obesity effects. The down-regulation of lipogenesis-related genes (fas cell surface death receptor (FAS), stearoyl-CoA desaturase 1 (SCD1), and sterol regulatory element-binding protein 1c (SREBP-1c)) and upregulation of lipid oxidation-related genes (peroxisome proliferator-activated receptor-α (PPAR-α), liver X receptor-α (LXR-α), adenosine monophosphate-activated protein kinase (AMPK), peroxisome proliferator-activated receptor-gamma coactivator-1α (PGC-1α), and adiponectin receptor 1) are the most obvious evidence of the antilipidemic effects of astaxanthin (Wang et al., 2021). Astaxanthin intervention in mice fed a high-fat diet reduced body weight as well as liver and plasma triglyceride and total cholesterol levels. It also decreased carbohydrate utilization and increased fatty acid oxidation during exercise through decreased oxidative modification of carnitine palmitoyl transferase-1 (CPT-1) (Aoi et al., 2008; Ikeuchi et al., 2007). In addition to hyperlipidemia, its effects on hypertension and

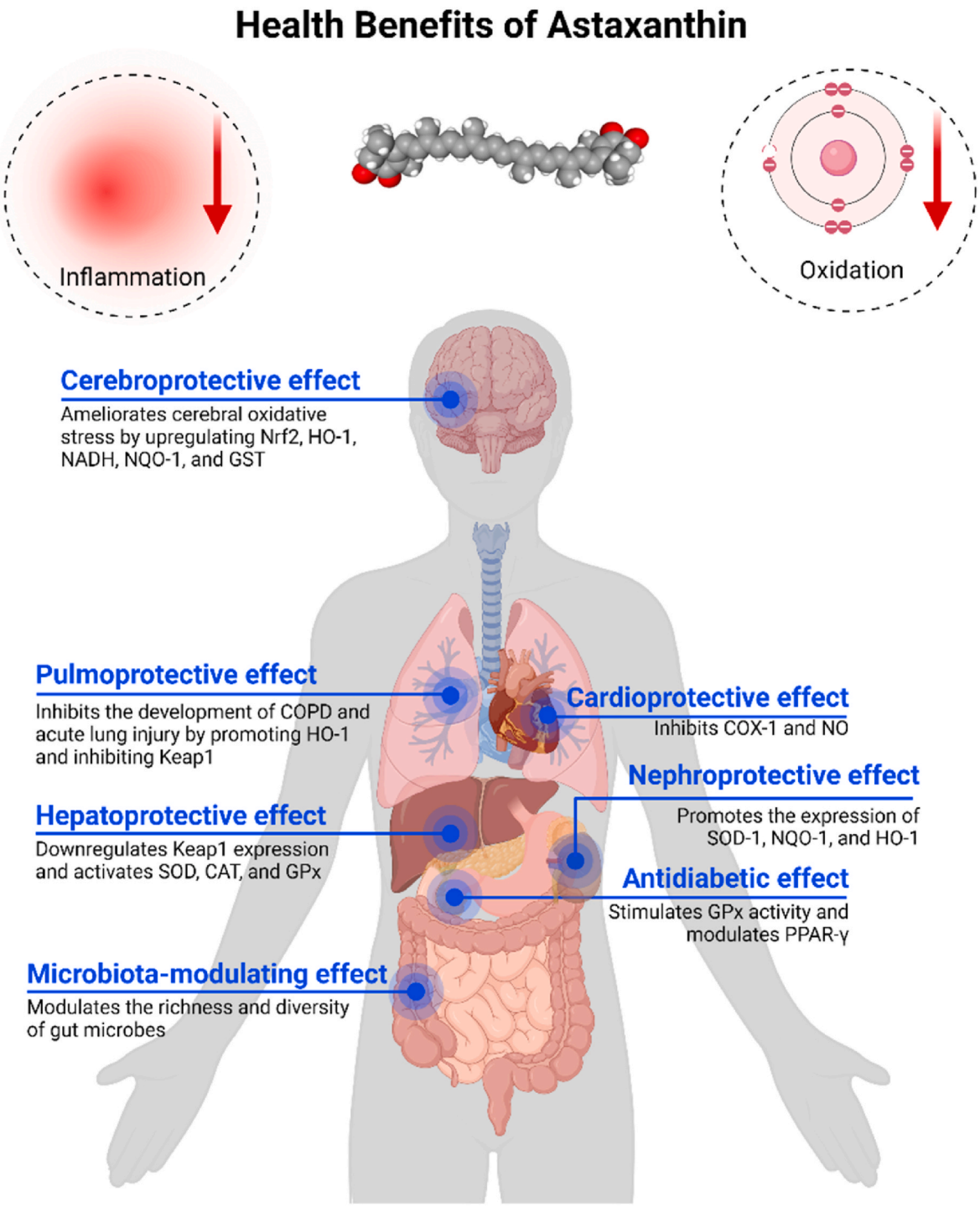

Fig. 2. Organ-level health effects of astaxanthin in relation to molecular pathways.

hyperglycemia are also promising. Astaxanthin has been reported to reduce the risk of stroke by improving blood pressure in spontaneously hypertensive rats (Hussein et al., 2005a). It also decreased NO levels and increased cyclic guanosine acid, associated with smooth muscle relaxation. As a result, the level of elastin in the aorta was reduced. With the decrease in wall thickness, the lumen expanded and blood pressure improved (Hussein et al., 2006). Astaxanthin delayed carbohydrate digestion and absorption by decreasing the activity of α-glucosidase enzyme and thus prevented postprandial hyperglycemia (Du et al., 2020). The enzymes extracellular signal-regulated kinase (ERK) and c-Jun N-terminal kinase (JNK) play important roles in insulin resistance. Astaxanthin has been reported to reduce insulin resistance by down-regulating both ERK and JNK (Bhuvaneswari and Anuradha, 2012).

Astaxanthin exerts anti-cancer effects through different mechanisms. First, it shows anti-tumor activity by reducing ROS levels. At the same time, it has pro-oxidant activity in cancer cells with high ROS concentrations. It also activates tumor suppressor proteins such as p53 (Shin et al., 2020). Another anti-cancer effect is based on inhibiting cell proliferation and inducing apoptosis (Li et al., 2015). In addition, astaxanthin may reduce the growth of cancer cells by affecting matrix metalloproteinases (MMPs). MMPs, and especially the type IV collagenase MMP-9, destroy almost all components of the matrix surrounding

cancer cells. Thus, they cause both the growth of cancerous tissue and its invasion into surrounding connective tissues (Herszényi et al., 2012). Astaxanthin has been shown to reduce glioblastoma migration and invasion by downregulating MMP-2 and MMP-9 (Siangcham et al., 2020).

Another notable health benefit of astaxanthin is its anti-aging effect. Mitochondrial oxidative damage underlies the mitochondrial theory of aging (Lee and Wei, 2012). Astaxanthin has been reported to stabilize the mitochondrial membrane and increase the adenosine triphosphate (ATP) in the mitochondria of leukocytes (Liu et al., 2020; Park et al., 2013). It was also found to reverse the decreased activities of mitochondrial respiratory chain complexes with aging (Liu et al., 2020).

1.3. Astaxanthin's effects on the nervous system

Astaxanthin has the ability to easily cross the blood-brain barrier thanks to its highly suitable structure (Grimmig et al., 2017b). Therefore, the most important target organ of astaxanthin is thought to be the brain (Galasso et al., 2018). The effects of this anti-inflammatory and anti-apoptotic molecule on the pathophysiology of neurodegenerative conditions have recently become topics of interest. Astaxanthin is recognized as a multi-target neuroprotective agent due to these effects discovered in recent years (Bahbah et al., 2021).

The central nervous system (CNS) can activate innate immunity in response to various neurodegenerative conditions. During neurodegeneration processes, a local neuroinflammatory response occurs, leading to the mobilization and activation of innate immune cells. The main CNS cell types involved in neuroinflammation are microglia, astrocytes, vascular cells, neutrophils, and macrophages (Masgrau et al., 2017). In particular, microglia cells, the resident macrophages of the brain, are urgently activated by neurodegenerative invading pathogens or cellular damage and release proinflammatory cytokines such as TNF-α, IL-6, and NO. These cytokines initially function well in neutralizing neurodegenerative threats. However, chronic microglial activation and proinflammatory cytokine responses are cytotoxic to the CNS. Moreover, this immune response is dysregulated with aging. Basal levels of proinflammatory cytokines may be elevated in the CNS even in the absence of any neurodegenerative hazard (Ekdahl et al., 2003; Lynch, 2010). Astaxanthin, which has obvious anti-inflammatory effects, is likely to attenuate chronic microglial activation and *in vitro* studies have reported that lipopolysaccharide-induced microglial IL-6, COX-2, and inducible nitric oxide synthase (iNOS)/NO expression and release were reduced by astaxanthin (Choi et al., 2011; Kim et al., 2010b). The most important factor characterizing neurodegenerative conditions is cerebral oxidative stress, and chronic microglial activation is an important source of ROS. The reduction of microglial oxidative stress by the important antioxidant astaxanthin may also be a neuroprotective scenario (Koutsilieri et al., 2002). As astaxanthin appears to modulate microglia cells by alleviating both microglial activation-induced inflammation and oxidative stress (Grimmig et al., 2017b).

Astaxanthin may also enhance neurogenesis and neuroplasticity. *In vitro* and *in vivo* studies showed that it promotes the proliferation of neural progenitor cells (NPCs) (Kim et al., 2010a; Yook et al., 2016). It was also demonstrated that astaxanthin protects NPCs against oxidative damage and limits the apoptotic cascade (Kim et al., 2009). Astaxanthin-promoted neurogenesis was shown to improve spatial memory performance associated with the hippocampus in different studies (Hussein et al., 2005b; Xu et al., 2015; Yook et al., 2016). In addition, astaxanthin has been reported to have the capacity to modulate ERK signaling (Kim et al., 2010b). Astaxanthin-induced ERK pathway activation may increase the transcription of antioxidant defense mechanism components by promoting Nrf2 release. This suggests another neuroprotective mechanism by which astaxanthin may act on the CNS (Li et al., 2013). Another factor associated with age-related spatial memory impairment is a decrease in the level of brain-derived neurotrophic factor (BDNF) (Wibrand et al., 2013; Wu et al., 2014b). BDNF is an important neurotrophin with the potential to modulate neurogenesis and synaptic transmission. It has been reported that BDNF may promote synaptic plasticity by activating the ERK pathway (Stranahan and Mattson, 2012; Wu et al., 2014b). There is evidence that astaxanthin may upregulate BDNF (Wibrand et al., 2013; Wu et al., 2014b).

The potential health effects of astaxanthin have become a trending topic that has attracted the attention of neuroscientists in the last decade. There is evidence of the efficacy of astaxanthin against neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, and cerebral ischemia, in which oxidative stress mechanisms play a major role in the disease pathogenesis (Bahbah et al., 2021) (Fig. 3). Therefore, in this review we provide a comprehensive analysis of the preventive and therapeutic effects of astaxanthin on some neurodegenerative conditions.

2. Materials and methods

This systematic review included studies investigating the effects of astaxanthin on neurological or neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, multiple sclerosis, cerebrovascular diseases, and spinal cord injury. Owing to the medical nature of the question, the search was confined to the Web of Science, Scopus, PubMed, and Google Scholar databases. The search was filtered to include only articles published in the last 20 years and a total of 7329 articles were found among these databases. The search did not include book chapters or conference papers. EndNote referencing software (EndNote Version 20, Clarivate Analytics, Philadelphia, PA, USA) was used for deduplication. The number of articles excluded due to duplication was 1226. The inclusion criteria for articles were as follows: 1) being designed as an experimental (*in vitro* or *in vivo*) or human study; 2) having the full text available; 3) emphasizing astaxanthin and at least one neurodegenerative condition (Alzheimer's disease, Parkinson's disease, multiple sclerosis, cerebrovascular diseases, or spinal cord injury) in the title or abstract; 4. containing findings on the protective or therapeutic effects of astaxanthin against neurodegenerative conditions in the full text.

After the deduplication process, case reports, editorials, and review articles were also excluded. Of all accessed documents, 4322 were reviews, 268 were editorials, and 201 were case reports. Of the remaining 1312 articles, 93 were excluded because of a lack of the full text and 902 were excluded after reviewing title and abstract. Thus, 317 articles were considered for a full review. All of the texts that were fully reviewed were published in English. Therefore, it was not necessary to set the use of non-English languages as an exclusion criterion. After a careful screening process, 59 of the articles were deemed appropriate, and underwent review (Fig. 4). All of these eligible studies were experimental and did not include any human studies (clinical trials or cohort studies). The search terms included combination of "Astaxanthin" with "Alzheimer," "Parkinson," "Multiple Sclerosis," "Cerebrovascular Diseases," and "Spinal Cord Injury."

3. Preventive and therapeutic effects of astaxanthin against neurodegenerative diseases

3.1. Astaxanthin and Alzheimer's disease

Alzheimer's disease, first described by Alois Alzheimer in 1906, is a chronic neurodegenerative disease characterized by impaired memory and cognitive functions caused by neuronal loss in the neocortex and hippocampus (Karlawish et al., 2017). It is the most common type of dementia and there are still unknowns regarding its pathophysiology (Irvine et al., 2008). It is estimated that approximately 55 million people have dementia today, and patients with Alzheimer's disease constitute 60–70% of this population (WHO, 2023). Excessive accumulation of β-amyloid (Aβ) peptide in the cerebral cortex and hippocampus as a result of an imbalance of synthesis and clearance is typical of the disease

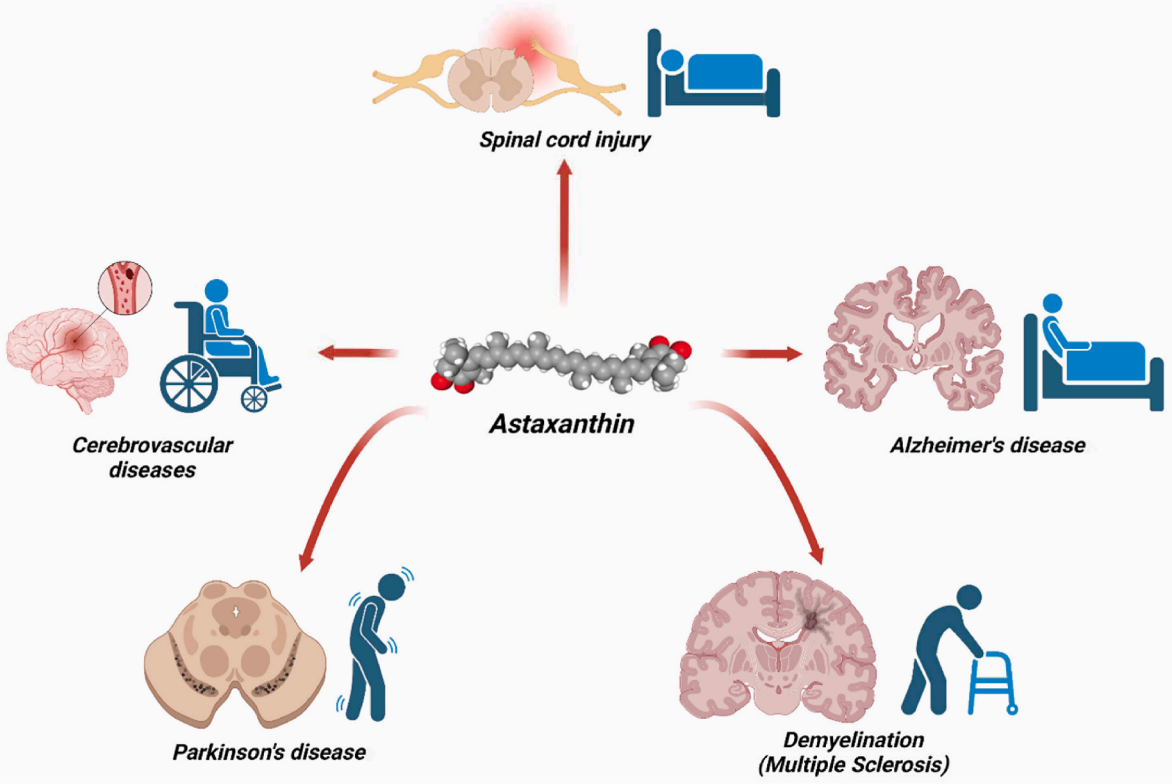

Fig. 3. Effects of astaxanthin on neurodegenerative conditions.

(Irvine et al., 2008; Wildsmith et al., 2013). While Aβ accumulation occurs in extracellular senile plaques, there is an accumulation of tau filaments in intracellular neurofibrillary tangles (Rahman and Lendel, 2021). In addition, an excess of damaged mitochondria has been found in neurons of patients with Alzheimer's disease. This is thought to be caused by mitochondrial DNA (de la Monte and Wands, 2006). Together with plaque and tangle accumulation and mitochondrial dysfunction, cerebral amyloid angiopathy (CAA), synaptic failure, oxidative damage, and neuroinflammation also play major roles in the pathophysiology of the disease (Rahman and Lendel, 2021). Therefore, therapeutic and preventive antioxidant therapy may be useful to support endogenous antioxidant defense (Hatziagapiou et al., 2019; Nakajima and Ohizumi, 2019; Wojsiat et al., 2018).

There are limited *in vitro* studies focusing on the effects of astaxanthin on Alzheimer's-related pathological changes (Table 1). Wang et al. (2010) used the SH-SY5Y human neuroblastoma cell line to examine the molecular effects of astaxanthin. In that study, astaxanthin was shown to induce antioxidant HO-1 expression through the ERK1/2 pathway and ameliorate Aβ-induced oxidative stress and apoptosis. Wen et al. (2017) showed that astaxanthin suppressed neuroinflammation by inhibiting NF-κB and JNK signaling in the BV2 murine microglial cell line. Babalola et al. (2023) reported that astaxanthin increased Aβ clearance, promoted anti-inflammatory protein synthesis, and decreased proinflammatory cytokine levels by inducing autophagy in a porcine brain capillary endothelial cell (pBCEC) culture. Liu et al. (2023a) found that astaxanthin suppressed oxidative stress-induced senescence via the SIRT1/PGC-1α signaling pathway on neuronal PC12 (pheochromocytoma-derived cells) culture used to study neurodegenerative diseases such as Alzheimer and Parkinson.

The results of *in vivo* studies reporting the therapeutic and preventive effects of astaxanthin on the pathology of Alzheimer's disease are also highly promising (Table 2). Al-Amin et al. (2016) showed that a 42-day astaxanthin intervention at a dose of 20 mg/kg improved spatial memory impairment in an aluminum chloride-induced Alzheimer's disease model. Che et al. (2018) used APP/PS1, a double transgenic mouse model expressing chimeric mouse/human amyloid precursor protein (Mo/HuAPP695swe) and mutant human presenilin-1 (PS1-dE9), to evaluate the effects of astaxanthin on Alzheimer's disease. A 60-day intervention of 0.2% docosahexaenoic acid-acylated astaxanthin added to the diets of the mice was reported to provide superior improvement on memory and learning deficits, tau hyperphosphorylation, neuroinflammation, oxidative stress, and inflammasomes. Using another transgenic animal model expressing amyloid precursor protein, Fanaee-Danesh et al. (2019) reported that six-days of astaxanthin treatment at a dose of 80 mg/kg increased the clearance of Aβ peptides from cerebrovascular endothelial cells, stabilized cholesterol homeostasis, and improved the blood-brain barrier. Taksima et al. (2019) showed that an astaxanthin intervention at a dose of 10 mg/kg for 30 days improved oxidative stress and reduced cognitive and spatial memory impairments in an Aβ-induced model of Alzheimer's disease. Han et al. (2019) found that an astaxanthin intervention at a dose of 50 mg/kg for four weeks inhibited lipopolysaccharide-induced amyloidogenesis and oxidation and reduced neuroinflammation by blocking STAT3 activity in a lipopolysaccharide-induced Alzheimer's disease model. In another study by Al-Amin et al. (2019) evaluating scopolamine-induced Alzheimer's disease, a toxin-induced experimental model, it was reported that 28-day astaxanthin treatment at a dose of 2 mg/kg prevented oxidative damage in striatal-hippocampal cholinergic neurons. Hongo et al. (2020) utilized APP^{NL-G-F} mice for a novel transgenic Alzheimer's disease model. They found that Aβ42 deposition and phosphorylated tau (p-tau) formation were significantly decreased, while glutathione biosynthesis and parvalbumin-positive neuron density were increased in mice fed a diet containing 0.02% astaxanthin for approximately 7.5 months. Hafez et al. (2021) examined the efficacy of a 6-week astaxanthin treatment at different doses (5, 10, and 15 mg/kg) in an Alzheimer's disease model induced by hydrated aluminum chloride injection. They found that the therapeutic effects of astaxanthin on Alzheimer's disease-related pathologies such as increased oxidative

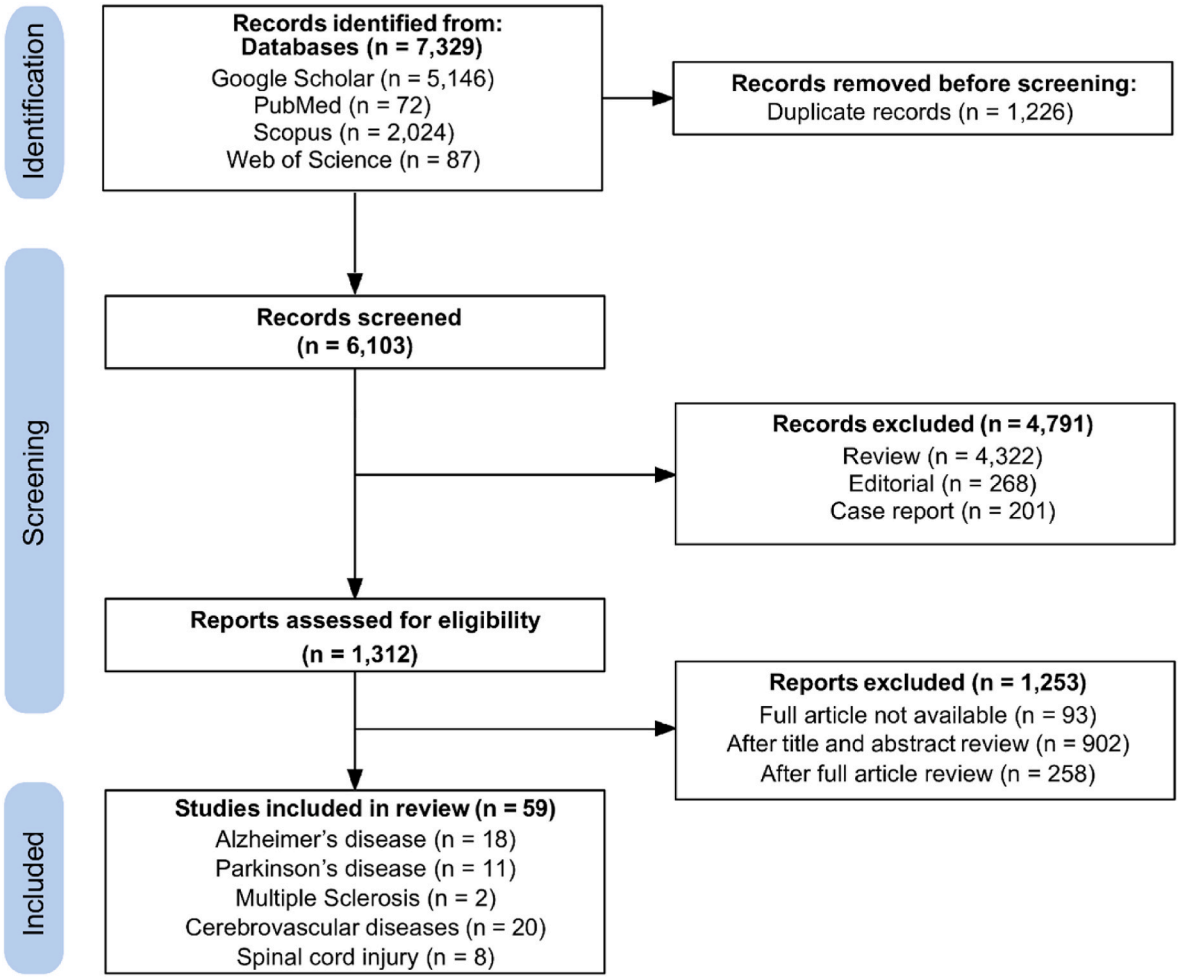

Fig. 4. Flow diagram of literature search.

stress, impaired cholinergic and serotonergic neurotransmissions, decreased microRNA 124 (miR-124) expression, and increased microglial activation were heightened as the dose increased. Chen et al. (2021) used an intraventricular infusion of ferrous amyloid buthionine to model an Alzheimer's disease-like condition in rats. Astaxanthin at a dose of 10 mg/kg given by intraperitoneal injection for seven days was reported to improve neuroinflammatory response, cholinergic fiber loss, spine loss, and spatial memory impairment. Huang et al. (2021) found that astaxanthin intervention at a dose of 10 mg/kg for 21 days improved cognitive function in APP/PS1 double-transgenic mice by activating the mTOR pathway, which is essential for synaptic plasticity, thereby increasing memory and learning capacity. They also observed increased Aβ-degrading enzymes and mitochondrial fusion. Lotosh et al. (2022) found that treating 5xFAD mice, constituting a transgenic model characterized by severe amyloid pathology, with astaxanthin or its esters at a dose of 2 mg/kg for two months improved locomotor activity and anxiety-like behaviors. Shehata et al. (2023a), studied a hydrated aluminum chloride-induced model of Alzheimer's disease, reported that treatment with nanostructured lipid carriers co-loaded with donepezil and astaxanthin decreased the levels of NF-κB, malondialdehyde (MDA), caspase-3, Aβ1-42, and acetylcholinesterase and increased the levels of glutathione and acetylcholine in the cortex and hippocampus more than treatment with nanostructured lipid carriers loaded with only donepezil. In another report, the same research group stated that astaxanthin (nanostructured lipid carriers loaded with only astaxanthin) treatment at a dose of 0.4 mg/kg for 30 days improved cholinergic neurotransmission and reduced neuroinflammation, oxidative stress, and apoptosis, while also suppressing the amyloidogenic pathway in the same Alzheimer's disease model (Shehata et al., 2023b). Paramakrishnan et al. (2023) showed that 21 days of astaxanthin intervention at low (10 mg/L) and high (20 mg/L) doses prevented amyloid protein deposition, reversed neuronal nitrite, and inhibited acetylcholinesterase activity in a streptozotocin-induced zebrafish model of Alzheimer's disease. The high dose astaxanthin intervention inhibited MMP-13 activity. In the last of these *in vivo* studies evaluating the effects of astaxanthin intervention on Alzheimer's disease, it was reported that the treatment (10 mg/kg for 30 days) effectively inhibited Aβ-mediated oxidative stress-induced apoptosis of hippocampal neurons by acting on the SIRT1/PGC-1α signaling pathway, thus increasing memory and learning capacity (Liu et al., 2023a).

3.2. *Astaxanthin and Parkinson's disease*

Another age-related neurological condition is Parkinsonism, a multisystem neurodegenerative disease with both motor and non-motor features (Archibald et al., 2013; Bahbah et al., 2021). The disease has been reported to affect 0.1–0.2% of the population and the global prevalence is as high as 1% in people over 60 years of age. The motor symptoms of Parkinson's disease are arise from three main movement disorders: tremor, rigidity, and bradykinesia. Although postural instability is also a supportive finding in these patients, it was removed as the fourth diagnostic criterion with a recent revision (Kasten et al., 2007). Common non-motor symptoms include urinary dysfunction, constipation, psychosis, depression, and apathy (Church, 2021). The main neuropathological findings of the disease are Lewy bodies containing α-synuclein, loss of dopaminergic neurons, and destruction of

Table 1
Summary of *in vitro* studies evaluating the effect of astaxanthin on Alzheimer's disease.

Reference	Cell culture	Model	Dose	Key results
Wang et al. (2010)	SH-SY5Y	Alzheimer	1–20 μM	Astaxanthin induced antioxidant enzyme HO-1 expression in concentration-dependent and time-dependent manners through activation of ERK1/2 signaling pathways and thus ameliorate amyloid peptide-induced oxidative stress and apoptosis.
Wen et al. (2017)	BV2	Alzheimer	10 μM	Astaxanthin promoted microglia polarization of arginase, IL-10, and CD206 to suppress neuroinflammation via low-density lipoprotein receptor-related protein-1-dependent manner by inhibiting NF-κB and JNK signaling.
Babalola et al. (2023)	pBCEC	Alzheimer	10 μM	Co-incubation of astaxanthin with Aβ reduced Aβ production, induced autophagy, and enhanced Aβ clearance in pBCECs. Astaxanthin affected inflammation by the activating anti-inflammatory proteins and reducing the secretion of proinflammatory cytokines.
Liu et al. (2023a)	PC12	Alzheimer	10 μM	Astaxanthin suppressed oxidative stress-induced senescence in PC12 cells via the SIRT1/PGC-1α signaling pathway and acted as a protective agent against cytotoxic damage caused by Aβ.

BV2, Murine microglial cell line; **SH-SY5Y,** A cloned subline of a neuroblastoma cell line; **pBCEC,** Primary porcine brain capillary endothelial cells; **PC12,** Pheochromocytoma derived cells.

non-dopaminergic neurons in the substantia nigra (Kasten et al., 2007). α-Synuclein accumulation plays an important role in the progression of Parkinson's disease and is directly related to motor and non-motor symptoms. The nervous system components first affected in the pathological process are the dorsal motor nucleus of the vagus nerve, the anterior olfactory nucleus, and the locus coeruleus. The progressive pathology is last seen in the substantia nigra. Subsequently, cortical regions of the brain are damaged (Kwan and Whitehill, 2011).

Almost all genes involved in Parkinson's disease, including α-synuclein gene (SNCA), are known to be mediated by miRNAs (Leggio et al., 2017). SNCA is the main gene responsible for the early onset of Parkinson's disease. microRNA 7 (miR-7) reduction in the substantia nigra is associated with α-synuclein accumulation and dopaminergic neuron loss (Bahbah et al., 2021). Normal expression of miR-7 is important as it allows neurogenesis and maintains α-synuclein at physiological levels. miR-7 replacement therapy reverses oxidative stress, mitochondrial dysfunction, apoptosis, and inflammasomes by downregulating genes associated with Parkinson's disease, particularly SNCA (Titze--de-Almeida & Titze-de-Almeida, 2018).

In vitro studies investigating the pathophysiology of Parkinson's disease have generally used SH-SY5Y neuroblastoma and PC12 pheochromocytoma cell cultures because human dopaminergic neurons, which are directly damaged in cases of Parkinson's disease, are quite difficult to obtain and maintain. The SH-SY5Y cell line is preferred because it has catecholaminergic, although not fully dopaminergic, neuronal properties and is easy to maintain (Xicoy et al., 2017). The PC12 cell line, which can undergo neuronal differentiation in response to nerve growth factor (NGF), can also provide many of the postmitotic properties of dopaminergic neurons. The ability to directly model sympathetic neurons affected by Parkinson's disease makes the PC12 cell line advantageous (Malagelada and Greene, 2008).

Parkinson's disease, like other age-related neurodegenerative conditions, is closely associated with oxidative stress and inflammation (Elfil et al., 2021). Therapeutic and preventive effects of astaxanthin on pathophysiology of the disease have been demonstrated in many *in vitro* and *in vivo* studies (Tables 3 and 4). It has been reported that astaxanthin may act on the miR-7/SNCA axis and alleviate endoplasmic reticulum-induced stress (Shen et al., 2021). Ikeda et al. (2008) investigated the protective effects of astaxanthin on 6-hydroxydopamine (6-OHDA)-induced apoptosis in the SH-SY5Y cell line and found that apoptosis was suppressed by astaxanthin in a dose-dependent manner. Treatment also reversed mitochondrial dysfunction. Activation of p38 mitogen-activated protein kinase (p38 MAPK) plays a critical role in 6-OHDA-induced mitochondrial dysfunction and apoptosis. Astaxanthin blocked p38 MAPK phosphorylation. Liu et al. (2009) also examined the effect of astaxanthin on docosahexaenoic acid hydroperoxide (DHA-OOH) and 6-OHDA-mediated apoptosis in SH-SY5Y cells. Astaxanthin pretreatment inhibited the apoptosis, intracellular ROS generation, and mitochondrial abnormalities induced by both neurotoxins. Chan et al. (2009) used PC12 cells to examine the efficacy of astaxanthin against Parkinson's disease-associated oxidative damage. PC12 cells were exposed to hydrogen peroxide (H_2O_2) or 1-methyl-4-phenylpyridinium (MMP^+) ions after astaxanthin pretreatment. The pretreatment reduced H_2O_2- and MMP^+-induced apoptosis, DNA fragmentation, lactate dehydrogenase (LDH) release, and mitochondrial membrane potential decrease. Lee et al. (2011) reported that astaxanthin pretreatment reduced MMP^+-induced oxidative damage and apoptosis in human SH-SY5Y cells and that this protective effect was due to the increased expression of SOD, catalase, and (B-cell lymphoma 2) Bcl-2 and decreased expression of Bcl-2-associated X protein (Bax). Ye et al. (2012) reported that the heme oxygenase-1/nicotinamide adenine dinucleotide phosphate oxidase 2 (HO-1/NOX2) axis is involved in the mechanism by which astaxanthin protects PC12 cells from MMP^+-induced oxidative stress. In a different report, the same researchers emphasized that astaxanthin also suppresses the activated transcription factor 1/N-methyl-D-aspartate receptor subunit 1 (Sp1/NR1) signaling pathway in preventing MMP^+-induced oxidative damage in PC12 cells (Ye et al., 2013). Shen et al. (2021) found that astaxanthin not only inhibited MMP^+-induced apoptosis and endoplasmic reticulum stress but also ameliorated the dysregulation of miR-7 and SNCA expression in SH-SY5Y cells. Anguchamy and Muthuvel (2023), who aimed to investigate the *in vitro* protective effects of astaxanthin against Parkinson's disease, used a different cell line and a different toxicity model in their study. Using SK-N-SH human neuroblastoma cells, neurotoxicity was induced by rotenone, which inhibits mitochondrial complex I and triggers oxidative stress in dopaminergic neurons. Astaxanthin dose-dependently reduced rotenone-induced oxidative stress and mitochondrial dysfunction. Wang et al. (2023) used a paraquat-induced model to examine the anti-Parkinsonian effects of astaxanthin in SH-SY5Y cells. Paraquat-induced MAPK signaling was inhibited by astaxanthin, thereby suppressing oxidative stress and apoptosis.

Although fewer in number than *in vitro* studies, *in vivo* studies have also presented remarkable results regarding the anti-Parkinsonian effects of astaxanthin (Table 4). Lee et al. (2011), whose *in vitro* results were highlighted above, reported that astaxanthin intervention at a dose of 30 mg/kg for 12 weeks increased tyrosine hydroxylase-positive neurons and decreased argyrophilic neurons in a 1-methyl-4-phenyl-1, 2,3,6-tetrahydropyridine (MPTP)-induced model of Parkinson's disease. Grimmig et al. (2017a) reported that an astaxanthin intervention at a dose of 3 mg/kg for four weeks increased the number of tyrosine hydroxylase-positive neurons in the substantia nigra and striatum and also attenuated neuroinflammatory processes in an MPTP-induced Parkinson's disease model. Tyrosine hydroxylase, which catalyzes the synthesis of L-dihydroxyphenylalanine (L-Dopa), the rate-limiting reaction in dopamine synthesis, is known to be reduced in cases of Parkinson's disease (Tabrez et al., 2012). On the other hand, argyrophilic neurons are an early histopathological marker of brain injury (Ishida et al., 2004). Therefore, the positive effects of astaxanthin on tyrosine

Table 2
Summary of *in vivo* studies evaluating the effect of astaxanthin on Alzheimer's disease.

Reference	Model	Intervention	Animals	Key results
		(I) Dose (II) Duration (III) Administration	(I) Genus (II) Age (III) Gender	
Al-Amin et al. (2016)	Aluminum chloride-induced spatial memory impairment	(I) 20 mg/kg/day (II) 42 days (III) Oral gavage	(I) Swiss mice (II) 4 months (III) Male	Astaxanthin improved aluminum-induced impaired memory performances presumably by the reduction of oxidative stress in the distinct brain regions.
Che et al. (2018)	APP/PS1 double-transgenic mice	(I) 0.2% in mice chow (II) 60 days (III) In chow	(I) Transgenic mice (II) 3 months (III) Male and female	Docosahexaenoic acid -acylated astaxanthin diesters was superior to free astaxanthin in reducing tau hyperphosphorylation, suppressing neuroinflammation, regulating the parameters of oxidative stress, and inflammasome expression and activation as well as in memory and learning improvement in APP/PS1 mice.
Fanaee-Danesh et al. (2019)	Triple transgenic 3xTg AD mice harbouring the mutant genes APP $_{Swe}$/MAPT $_{P301L}$/PSEN1 $_{M146V}$	(I) 80 mg/kg/day (II) 6 days (III) Oral gavage	(I) Transgenic mice (II) 32–49 or 68-92 weeks (III) Female	Astaxanthin improved blood-brain barrier by enhancing clearance of Aβ peptides from cerebrovascular endothelial cells and balancing cholesterol homeostasis.
Taksima et al. (2019)	Aβ-induced model	(I) 10 mg/kg/day (II) 30 days (III) Oral gavage	(I) Wistar rats (II) 2 months (III) Male	Astaxanthin reduced oxidative stress and reversed cognitive and spatial memory impairments.
Han et al. (2019)	Lipopolysaccharide -induced neuroinflammation, oxidative stress and memory dysfunction	(I) 30 and 50 mg/kg/day (II) 4 weeks (III) Oral gavage	(I) ICR mice (II) 8 weeks (III) Male	Astaxanthin inhibited lipopolysaccharide-induced amyloidogenesis, oxidant activity, and neuroinflammatory response via the blocking of STAT3 activity through direct binding.
Al-Amin et al. (2019)	Scopolamine-induced spatial memory deficit model	(I) 2 mg/kg/day (II) 28 days (III) Oral gavage	(I) Swiss albino mice (II) 10 weeks (III) Male	Astaxanthin treatment prevented scopolamine-induced oxidative damage in striatal-hippocampal cholinergic neurons.
Hongo et al. (2020)	APP^{NL-G-F} mice	(I) 0.02% in mice chow (II) From 5-to-6 weeks to 9 months old (III) In chow	(I) Transgenic mice (C57BL/6J) (II) 2 months (III) Male	Astaxanthin significantly reversed Alzheimer's disease pathological processes (p-tau formation, Aβ42 deposition, glutathione decrease, and parvalbumin-positive neuronal deficits) and ameliorated memory deficits.
Hafez et al. (2021)	Hydrated aluminum chloride-induced Alzheimer's Disease like model	(I) 5, 10, and 15 mg/kg/day (II) 6 weeks (III) Oral gavage	(I) Rats (albino) (II) 3 months (III) Male	Astaxanthin showed dose-dependent therapeutic effects on multiple pathways that play key roles in the development and progression of Alzheimer's disease, including oxidative stress, impaired cholinergic and serotonergic neurotransmissions, suppressed miR-124 expression, and microglial activation.
Chen et al. (2021)	Ferrous amyloid buthionine infused sporadic model	(I) 1 and 10 mg/kg/day (II) 7 days (III) Intraperitoneal injection	(I) Sprague-Dawley rats (II) 3-4 months (III) Male	Astaxanthin was found to reverse the neuroinflammatory responses, spatial memory impairment, and spine and cholinergic fiber loss in the hippocampus.
Huang et al. (2021)	APP/PS1 double-transgenic mice	(I) 10 mg/kg/day (II) 21 days (III) Oral gavage	(I) Transgenic mice (II) 8 months (III) Male	Astaxanthin ameliorated cognitive deficits by activating the mTOR pathway which is necessary for synaptic plasticity, leading to improved memory and learning. It also increased Aβ-degrading enzymes and mitochondrial fusion.
Lotosh et al. (2022)	5xFAD transgenic mice	(I) 2 mg/kg/day (II) 2 months (III) Oral gavage	(I) Transgenic mice (II) 4-6 months (III) Male	Both astaxanthin and its esters improved the behavioral parameters in the elevated plus maze (anxiety) and open field (locomotor activity) tests.
Shehata et al. (2023a)	Hydrated aluminum chloride-induced model	(I) 0.4 mg/kg/day (II) 6 weeks (III) Intranasal	(I) Rats (albino) (II) 3 months (III) Male	Nanostructured lipid carriers co-loaded with donepezil and astaxanthin showed significantly higher antioxidant, anti-apoptotic, anti-amyloidogenic, anti-inflammatory, and anti-acetylcholinesterase effects than nanostructured lipid carriers loaded with only donepezil.
Shehata et al. (2023b)	Hydrated aluminum chloride-induced model	(I) 0.4 mg/kg/day (II) 30 days (III) Intranasal	(I) Rats (albino) (II) 3 months (III) Male	Intranasal treatment of astaxanthin-loaded nanostructured lipid carriers improved the cholinergic neurotransmission, decreased neuroinflammation, oxidative stress, and apoptosis, and also suppressed the amyloidogenic pathway.
Paramakrishnan et al. (2023)	Streptozotocin-induced cerebrovascular damage-associated Alzheimer's disease	(I) 10 and 20 mg/L (II) 21 days (III) Dissolved in aquarium water	(I) Zebrafish (II) 8 months (III) Male	Astaxanthin treatment at both doses improved tissue extravasation and blood glucose regulation, prevented amyloid protein accumulation, reversed neuronal nitrite, and inhibited acetylcholinesterase activity.
Liu et al. (2023a)	Aβ-induced model	(I) 10 mg/kg/day (II) 30 days (III) Oral gavage	(I) ICR mice (II) 6 weeks (III) Male	Astaxanthin effectively inhibited Aβ-mediated oxidative stress-induced apoptosis of hippocampal neurons by acting on the SIRT1/PGC-1α signaling pathway, thereby improving memory and learning capacity.

APP/PS1, Amyloid Precursor Protein-Presenilin 1; **3xTg AD,** Triple transgenic Alzheimer's disease; **APP^{NL-G-F},** Amyloid precursor protein knock-in mouse model; **5XFAD,** Mouse model of amyloid deposition with five familial Alzheimer's disease mutations.

Table 3
Summary of *in vitro* studies evaluating the effect of astaxanthin on Parkinson's disease.

Reference	Cell culture	Model	Dose	Key results
Ikeda et al. (2008)	SH-SY5Y	6-OHDA-induced apoptosis	1, 5, 10, and 20 μM	Astaxanthin suppressed apoptosis in a dose-dependent manner, inhibited mitochondrial dysfunction, blocked p38 MAPK phosphorylation, and eliminated reactive oxygen species.
Liu et al. (2009)	SH-SY5Y	ROS-mediated apoptosis (DHA-OOH and 6-OHDA)	25, 50, 100, 500, and 1000 nM	Astaxanthin pretreatment inhibited apoptosis, intracellular reactive oxygen species generation, and mitochondrial abnormalities.
Chan et al. (2009)	PC12	H_2O_2- or MPP^+-induced cell injury	10 and 20 μM	Astaxanthin pretreatment reduced apoptosis, DNA fragmentation, and LDH release, and also prevented mitochondrial membrane potential decrease.
Lee et al. (2011)	SH-SY5Y	MPP^+-induced mitochondrial dysfunction	50 μM	Astaxanthin attenuated oxidative damage and apoptosis. It increased SOD, catalase, and Bcl-2 expressions and decreased Bax expression.
Ye et al. (2012)	PC12	MPP^+-induced oxidative damage	5, 10, 20 μM	Astaxanthin suppressed MPP^+-induced oxidative stress via HO-1/NOX2 axis.
Ye et al. (2013)	PC12	MPP^+-induced oxidative damage	1.25, 2.5, 5, 10, and 20 μmol/L	Astaxanthin inhibited MPP^+-induced oxidative stress via the Sp1/NR1 signaling pathway.
Shen et al. (2021)	SH-SY5Y	MPP^+-induced apoptosis promotion	5, 10, 25 and 50 μM	Astaxanthin treatment inhibited MPP^+-induced apoptosis and endoplasmic reticulum stress and reversed the dysregulation of miR-7 and SNCA expression.
Anguchamy and Muthuvel (2023)	SK-N-SH	Rotenone-induced neurotoxicity	5, 10, 15, 20, 25, and 30 nM	Astaxanthin treatment attenuated rotenone-induced cytotoxicity, oxidative stress, and mitochondrial dysfunction in a dose-dependent manner.
Wang et al. (2023)	SH-SY5Y	Paraquat-induced neuron damage	5 ng/mL	Astaxanthin enhanced cell survival against paraquat toxicity by suppressing oxidative stress and apoptotic cell death.

SH-SY5Y, A cloned subline of a neuroblastoma cell line; **6-OHDA,** 6-hydroxydopamine; **DHA-OOH,** docosahexaenoic acid hydroperoxide; **MPP^+,** 1-methyl-4-phenyl-pyridine; **SK-N-SH,** Human neuroblastoma cell line; **PC12,** Pheochromocytoma derived cells.

Table 4
Summary of *in vivo* studies evaluating the effect of astaxanthin on Parkinson's disease.

Reference	Model	Intervention	Animals	Key results
		(I) Dose (II) Duration (III) Administration	(I) Genus (II) Age (III) Gender	
Lee et al. (2011)	MPTP-induced model	(I) 10 and 30 mg/kg/day (II) 28 days (III) Intraperitoneal injection	(I) C57BL/6 mice (II) 12 weeks old (III) N/A	Astaxanthin reversed the decrease in tyrosine hydroxylase-positive neurons and increase in argyrophilic neurons.
Grimmig et al. (2017a)	MPTP-induced model	(I) 3 mg/kg/day (II) 4 weeks (III) In chow	(I) C57BL/6 mice (II) 3 months (III) Male	Astaxanthin treatment increased the number of tyrosine hydroxylase-positive neurons, alleviated neuroinflammation, and reduced IBA1 levels in the substantia nigra and striatum, thus attenuating microglial activation.
Grimmig et al. (2018)	MPTP-induced model	(I) 30 mg/kg/day (II) 5 weeks (III) In chow	(I) C57BL/6J mice (II) 3 or 18 months old (III) Male	Astaxanthin protected neurons in the substantia nigra from MPTP-induced apoptosis but was less effective in aged mice.
Wang et al. (2023)	Paraquat-induced model	(I) 30 mg/kg/day (II) 7 weeks (III) Intragastric injection	(I) C57BL/6J mice (II) 6 weeks (III) Male	Astaxanthin showed a strong protective effect on antagonized apoptotic cell death and oxidative stress. It also improved reduced range of motion and motor incoordination.

MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; **N/A,** Not available.

hydroxylase-positive and argyrophilic neurons in the substantia nigra are noteworthy. Astaxanthin also reduced ionized calcium-binding adapter molecule 1 (IBA1) levels in these tissues, thus attenuating microglial activation. In another study (Grimmig et al., 2018), the same researchers compared young (three months old) and old (18 months old) mice to evaluate the protective efficacy of an astaxanthin intervention in the MPTP-induced model. The astaxanthin intervention reduced apoptosis in the substantia nigra of both groups, but it was less effective in old mice. Wang et al. (2023) reported that an astaxanthin intervention at a dose of 30 mg/kg for seven weeks ameliorated paraquat-induced reduced range of motion and motor incoordination in the *in vivo* phase of their study. The findings of all these *in vitro* and *in vivo* studies suggest that astaxanthin intervention may represent co-adjuvant therapy against Parkinson's disease.

3.3. Astaxanthin and multiple sclerosis

Multiple sclerosis (MS), an autoimmune disease, is a non-traumatic chronic inflammatory condition that often affects young adults. Two pathological features underlie the disease: 1) inflammation with demyelination and 2) gliosis (astroglial proliferation) and neurodegeneration. MS manifests only in the CNS and does not spread to the peripheral nervous system. Some patients show progression from onset (primary progressive MS), but the majority of patients have secondary progressive MS, which is characterized by a gradual worsening as well as decreasing relapses (Hauser and Cree, 2020).

The primary cause of demyelination, which is the most important factor involved in the pathogenesis of MS, is oligodendrocyte death due to focal immune cell infiltration. Therefore, potent antioxidants may be potential co-adjuvant treatment agents to prevent oligodendrocyte death and reduce other complications associated with demyelination (Lotfi et al., 2021). There are no *in vitro* or clinical studies examining the therapeutic and preventive effects of astaxanthin on MS. On the other hand, there are only two studies on the efficacy of astaxanthin in laboratory animals with experimental MS models (Table 5). In the first of these studies, Bidaran et al. (2018) used the oligodendrocyte glycoprotein-induced autoimmune encephalomyelitis model to examine the possible effects of astaxanthin on MS pathology. Five weeks of astaxanthin intervention (0.4% added to chow) decreased the proinflammatory cytokine levels and increased anti-inflammatory cytokine

levels. Furthermore, the intervention increased the splenocyte proliferation index, and the ameliorative effects were also reflected in behavioral parameters. Lotfi et al. (2021) showed that astaxanthin treatment at a dose of 3 mg/kg for four weeks reduced oligodendrocyte death and myelin sheath damage and also improved basket behavior test results reflecting muscle strength in a cuprizone-induced MS model.

3.4. Astaxanthin and cerebrovascular diseases

Cerebrovascular diseases encompass a variety of conditions that alter the integrity of cerebral blood vessels, blood components, and hemodynamics, thereby disrupting normal cerebral blood flow. These include all causes of vascular brain injury such as cerebral atherosclerosis, aneurysms, vasculitis, chronic cerebral hypoperfusion, cerebral infarct, and hemorrhages (Owolabi et al., 2018). Cerebrovascular diseases, which usually manifest as acute cerebral infarction or subarachnoid hemorrhage, commonly result in ischemic or hemorrhagic stroke.

Acute cerebral infarction is a serious health condition that threatens human health and has high mortality rates (Lou et al., 2018). Oxidative stress, free radical damage, inflammation, neuronal apoptosis, excitatory amino acid toxicity, and impaired CNS metabolism have been reported to underlie the pathophysiological mechanisms of acute cerebral infarction (Nai et al., 2018). Inflammation, apoptosis, and oxidative stress have vital roles in the prognosis of the disease (Yang et al., 2021). Increased oxygen production in the brain suggests that oxidative stress underlies the mechanism of damage because the most important components of tissue damage after ischemic injury are ROS. Oxidative stress is known to be a major factor in the pathogenesis of ischemia-reperfusion injury. Therefore, antioxidant, anti-inflammatory, and anti-apoptotic approaches may provide support in preventing the poor prognosis of acute cerebral infarction (Nai et al., 2018).

The pathological basis of hemorrhage is vascular rupture, a consequence of frailty due to advanced age and high blood pressure. In intracerebral hemorrhage, leakage after rupture damages the brain parenchymal tissue (Iwata et al., 2018). On the other hand, in subarachnoid hemorrhage, blood flows into the subarachnoid space, triggering early brain injury (Qian et al., 2021). Early brain injury, the most common complication of subarachnoid hemorrhage, is the most important cause of hemorrhage-related mortality and morbidity (Sehba et al., 2012). The pathogenesis of early brain injury, which occurs within 72 h after subarachnoid hemorrhage and is characterized by lesions before cerebral vasospasm, includes hydrocephalus, ischemia, blood-brain barrier damage, autophagy of nerve cells, brain edema, and neuronal apoptosis (Cai et al., 2021; Qian et al., 2021). Despite advancements of medical technology, the morbidity and mortality caused by early brain injury have not been significantly reduced. Nevertheless, similar to studies on acute cerebral infarction, studies on early brain injury also emphasize apoptosis, inflammation, and oxidative stress (Cahill et al., 2006; Endo et al., 2007; Han et al., 2017). In particular, oxidative stress is the primary pathogenesis of cerebral vasospasm and early brain injury (Zhang et al., 2014c). Therefore, the development of antioxidative, anti-apoptotic, and anti-inflammatory approaches may represent an effective therapeutic strategy in hemorrhage and early brain injury (You et al., 2019; Zhang et al., 2014b, 2019).

A limited number of *in vitro* studies examining the effects of astaxanthin on cerebrovascular diseases have revealed promising findings. Using primary cortical neuron cultures obtained from the cortex of ICR mice embryos, Lu et al. (2010) examined the neuroprotective effects of different doses of astaxanthin (250–2000 nM) against H_2O_2-induced neuronal cell death. Astaxanthin attenuated H_2O_2-induced neuronal apoptosis and improved mitochondrial membrane potential, most notably at 500 nM. In another study conducted with immortalized mouse cerebral endothelial cells obtained from mice after ischemia-reperfusion, Kuo et al. (2019) examined the effects of astaxanthin on the expression of p75 neurotrophin receptor, one of the NGF receptors involved in the viability and apoptosis of neurons, and cell apoptosis. They exposed the cells to oxygen-glucose deprivation for 12 h to establish hypoxia and subsequently found that astaxanthin at a dose of 20 mM decreased p75 neurotrophin receptor expression and apoptosis in these cells (Table 6).

In vivo studies examining the preventive and therapeutic efficacy of astaxanthin against different cerebrovascular conditions such as cerebral ischemia, subarachnoid hemorrhage, and stroke provide a more comprehensive overview (Table 7). Many experimental studies on the effects of astaxanthin on cerebral ischemia have been reported in recent years. Shen et al. (2009) reported that a single dose of astaxanthin (20 μL, 0.1 mM) administered by intracerebroventricular injection before middle cerebral artery occlusion (MCAO) reversed the ischemia-mediated reduction of aconitase activity and reduced glutamate release, lipid peroxidation, cytochrome *c* translocation, and TUNEL labeling (apoptosis) in the ischemic cortex. Lu et al. (2010) compared astaxanthin treatments at double doses of 20 mg/kg, 50 mg/kg, and 80 mg/kg at 5 h and 1 h before ischemia in terms of cerebral infarct volume and neurological deficit score in the MCAO-induced cerebral ischemia model in the *in vivo* step of their study. They showed that astaxanthin treatments at doses of 50 mg/kg and 80 mg/kg reduced infarct volumes and improved neurological deficit scores. Xue et al. (2017) reported that astaxanthin treatment at a dose of 10 mg/kg for 28 days increased the number of surviving pyramidal neurons in the cornu ammonis 1 and 3 (CA1 and CA3) subfields of the hippocampus in a cerebral ischemia-reperfusion model induced by repeated occlusion of the bilateral common carotid artery (BCCAO). They also showed that the treatment increased glutathione and SOD levels and decreased MDA, cytochrome C, cleaved caspase-3, and Bax levels in the hippocampus, and also improved learning and memory deficits. Pan et al. (2017) reported that seven days of astaxanthin treatment (5 and 10 mg/kg) before

Table 5
Summary of *in vivo* studies evaluating the effect of astaxanthin on multiple sclerosis.

Reference	Model	Intervention	Animals	Key results
		(I) Dose (II) Duration (III) Administration	(I) Genus (II) Age (III) Gender	
Bidaran et al. (2018)	Oligodendrocyte glycoprotein-induced autoimmune encephalomyelitis	(I) 0.4% in mice chow (II) 5 weeks (III) In chow	(I) C57BL/6 mice (II) 6–8 weeks (III) Female	Astaxanthin reduced proinflammatory cytokine levels, splenocytes proliferation index and increased the anti-inflammatory cytokine levels.
Lotfi et al., 2021	Cuprizone-induced model	(I) 3 mg/kg/day (II) 4 weeks (III) Oral gavage	(I) Wistar rats (II) N/A (III) Male	Astaxanthin treatment reduced the myelin sheath disruption and oligodendrocyte damage.

N/A, Not available.

Table 6
Summary of *in vitro* studies evaluating the effect of astaxanthin on cerebrovascular diseases.

Reference	Cell culture	Model	Dose	Key results
Lu et al. (2010)	Primary cultured cortical neurons (cerebral cortex)	H_2O_2-induced apoptosis model	250–2000 nM	Astaxanthin reduced H_2O_2-induced (50 μM) apoptosis. Notably, 500 nM astaxanthin pretreatment greatly inhibited apoptosis and improved mitochondrial membrane potential.
Kuo et al. (2019)	Mouse immortalized cerebral endothelial cells	Ischemic-hypoxic-induced model	20 mM	Astaxanthin reduced apoptosis and p75 neurotrophin receptor expression, which plays a prominent role in endothelial cell death.

MCAO provided protection against ischemia. In that study, it was observed that both doses of astaxanthin reduced cerebral infarct volume, increased SOD levels and Nrf2 and HO-1 gene expressions, decreased MDA levels, inhibited neuronal apoptosis, and improved neurological functions. Nai et al. (2018) reported that astaxanthin treatment at different doses (20, 40, and 80 mg/kg) decreased the neurological deficit score, cerebral edema, and MDA level, whereas it increased the levels of antioxidant enzymes (catalase, SOD, and GPx) and BDNF and NGF expressions in the MCAO-induced cerebral infarction model. Wang et al. (2019a) showed that 28-day astaxanthin treatment (30 mg/kg) after MCAO improved balance, grip strength, and motor coordination and also increased growth-associated protein-43 (GAP-43) expression and axonal fiber number in the ischemic cortex. Yang et al. (2021) examined the neuroprotective efficacy of astaxanthin administration at a dose of 100 mg/kg for three days before MCAO. They found that astaxanthin improved neurological functions and reduced brain edema, cerebral infarct volume, and neuronal apoptosis. Astaxanthin also decreased inflammation, oxidative stress, and apoptosis and increased the levels of antioxidant parameters. Taheri et al. (2022) found that astaxanthin administration at different doses (25, 45, and 65 mg/kg) before and after MCAO reduced stroke volume, neurologic deficit scores, and lipid peroxidation. All doses increased GPx activity and relative catalase, SOD, and GPx gene expressions. Huo et al. (2022) reported that astaxanthin treatment at a dose of 10 mg/kg for seven days before MCAO reduced neurological severity scores and decreased neuroinflammation as measured by IL-1β, IL-6, and TNF-α levels in the brain. Park et al. (2022) showed that astaxanthin at a dose of 100 mg/kg administered for three days before BCCAO reduced ischemia-induced oxidative DNA damage, lipid peroxidation, and apoptosis in pyramidal cells in CA1 and CA3. They also found that the treatment reversed decreases in SOD1 and SOD2 expression in the same cells. In another study using the BCCAO model, two different doses (25 and 75 mg/kg) were compared to evaluate the efficacy of astaxanthin administered 15 min before ischemia. Both doses ameliorated ischemia-induced low SOD and catalase levels and high MDA levels (Yeğin et al., 2023). In summary, these studies emphasized that astaxanthin treatment reduced cerebral infarct volume, apoptosis, oxidative stress, and inflammation while improving learning and memory functions and neurological deficit scores in cerebral ischemia models.

The therapeutic and preventive effects of astaxanthin on subarachnoid hemorrhage are also quite remarkable (Table 7). Zhang et al. (2014a) reported that high-dose (75 mg/kg) astaxanthin administered orally 30 min after subarachnoid hemorrhage reduced the expression of proinflammatory cytokines and intercellular adhesion molecule-1 (ICAM-1) and decreased NF-κB activity. They stated that these effects may improve secondary brain injury components such as cerebral edema, blood-brain barrier dysfunction, and neuronal degeneration. The same researchers reported the therapeutic efficacy of astaxanthin (20 μL, 0.1 mM) injected into the left lateral ventricle after subarachnoid hemorrhage in a different study. It was stated that the treatment significantly increased phosphorylated Akt and Bad levels and decreased cleaved caspase-3 levels in the cortex after subarachnoid hemorrhage (Zhang et al., 2014b). In another study, they reported that astaxanthin given at the same dose and with the same administration method upregulated the expression of HO-1, NQO1, and GST-α1, which mediate the Nrf2-ARE pathway, in the cortex (Wu et al., 2014a). In their latest work on the effects of astaxanthin on subarachnoid hemorrhage, they reported that astaxanthin treatment (20 μL, 0.1 mmol) significantly reduced MMP-9 expression and activity after subarachnoid hemorrhage. MMP-9 is a key mediator of blood-brain barrier disruption in cases of cerebrovascular diseases. Released from glial and neuronal cells as well as endothelial cells and leukocytes, MMP-9 is activated by free radicals and other active MMPs. It disrupts the extracellular matrix of the blood-brain barrier, leading to edema and leukocyte leakage. This enhances the progressive inflammatory response to brain injury, known as secondary brain injury, hours or days after the initial cerebrovascular event. Considering the role of MMP-9 in the pathogenesis of secondary brain injury after subarachnoid hemorrhage, this molecular effect of astaxanthin is noteworthy (Zhang et al., 2015). In all four of these studies, the researchers noted that these molecular effects may ameliorate components of secondary brain injury such as cerebral edema, blood-brain barrier dysfunction, and neuronal degeneration. Wang et al. (2019b) reported that a single dose of astaxanthin (75 mg/kg) given 3 h after subarachnoid hemorrhage increased mitochondrial membrane potential, decreased the Bax/Bcl-2 ratio and caspase-3 activity, inhibited cytochrome C release, and partially improved cerebral expression of synaptic proteins and neurotrophins in the prefrontal cortex. Zhang et al. (2019) found that astaxanthin (20 μL, 0.1 mM) administered by ventricular injection 4 h after subarachnoid hemorrhage decreased TLR4 activation and inflammatory response, whereas it increased SIRT1 expression. Astaxanthin treatment also reduced brain edema and apoptosis and improved neurological function. Qian et al. (2021) showed that astaxanthin at a dose of 100 mg/kg injected into the lateral ventricle 30 min after subarachnoid hemorrhage decreased Bax levels and the expression of proinflammatory mediators (e.g., IL-6, IL-17, and TNF-α), increased Bcl-2 and anti-inflammatory IL-10 levels, inhibited neuronal apoptosis, and also decreased NOX2 levels, associated with thrombosis. In these *in vivo* studies of subarachnoid hemorrhage models, the protective and therapeutic efficacy of astaxanthin against apoptosis, oxidative stress, and inflammation were generally emphasized. In the only study examining the efficacy of astaxanthin in a traumatic brain injury model, Ji et al. (2017) showed that six days of high-dose astaxanthin treatment (75 mg/kg) after brain trauma improved sensorimotor coordination problems and spatial and non-spatial memory impairment in mice. The treatment also increased the levels of neuronal survival and plasticity-related parameters such as BDNF, GAP-43, synapsin, and synaptophysin in the cerebral cortex.

3.5. Astaxanthin and spinal cord injury

Spinal cord injury, one of the most common causes of disability and death, is characterized by the permanent loss of neurons and the disconnection of ascending and descending tracts, resulting in loss of sensory and motor function (Masoudi et al., 2017). It commonly occurs as a result of motor vehicle accidents and trauma, but it can also be caused by diseases (Snedecor et al., 2013). The pathology of spinal cord injury consists of two chronological phases: primary and secondary. The primary phase entails mechanical tissue injury characterized by damage

Table 7
Summary of *in vivo* studies evaluating the effect of astaxanthin on cerebrovascular diseases.

Reference	Model	Intervention	Animals	Key results
		(I) Dose (II) Duration (III) Administration	(I) Genus (II) Age (III) Gender	
Shen et al. (2009)	Cerebral ischemia/reperfusion (MCAO model)	(I) 20 μL, 0.1 mM (II) Single injection (III) Cerebroventricular injection	(I) Sprague-Dawley rats (II) N/A (III) Male	Astaxanthin increased ischemia-mediated aconitase activity and decreased glutamate release, lipid peroxidation, cytochrome C translocation, and apoptosis in ischemic cortex.
Lu et al. (2010)	Focal cerebral ischemia (MCAO model)	(I) 20, 50, 80 mg/kg/day (II) Twice (at 5 h and 1 h prior to ischemia) (III) Oral gavage	(I) Sprague-Dawley rats (II) N/A (III) Male	Astaxanthin pretreatment (5 h and 1 h before ischemia) dose-dependently reduced infarct volume and improved neurological deficit score.
Zhang et al. (2014a)	Subarachnoid hemorrhage (Pre-chiasmatic cistern blood injection model)	(I) 25 or 75 mg/kg (II) Single gavage (III) Oral gavage	(I) Sprague-Dawley rats (II) N/A (III) Male	Astaxanthin reduced NF-κB activity and downregulated the increased expression of inflammatory cytokines and ICAM-1 in both messenger RNA transcription and protein synthesis.
Zhang et al. (2014b)	Subarachnoid hemorrhage (Pre-chiasmatic cistern blood injection model)	(I) 20 μL, 0.1 mM (II) Single injection (III) Cerebroventricular injection (left lateral ventricle)	(I) Sprague-Dawley rats (II) N/A (III) Male	Astaxanthin treatment increased phosphorylated Akt and Bad levels and decreased cleaved caspase-3 levels in the cortex, thus attenuating apoptosis.
Wu et al. (2014a)	Subarachnoid hemorrhage (Pre-chiasmatic cistern blood injection model)	(I) 20 μL, 0.1 mM (II) Single injection (III) Cerebroventricular injection (left lateral ventricle)	(I) Sprague-Dawley rats (II) N/A (III) Male	Astaxanthin treatment attenuated early brain injury by increasing HO-1, NQO1, and GST-α1 expressions mediating the Nrf2-ARE pathway in the cortex.
Zhang et al. (2015)	Subarachnoid hemorrhage (Pre-chiasmatic cistern blood injection model)	(I) 20 μL, 0.1 mmol (II) Single injection (III) Cerebroventricular injection (left lateral ventricle)	(I) Sprague-Dawley rats (II) N/A (III) Male	Astaxanthin reduced activity and expression of MMP-9, leading to amelioration of brain edema and blood-brain barrier disruption.
Xue et al. (2017)	Repeated cerebral ischemia/reperfusion (BCCAO model)	(I) 10 mg/kg/day (II) 28 days (III) Intragastric injection	(I) ICR mice (II) 8 weeks (III) Male	Astaxanthin increased the number of surviving pyramidal neurons in CA1 and CA3 subfields of the hippocampus. It also increased glutathione and SOD levels, decreased MDA, cytochrome C, cleaved caspase-3, and Bax levels in the hippocampus, and improved learning and memory deficits.
Pan et al. (2017)	Stroke (MCAO model)	(I) 5 or 10 mg/kg/day (II) 7 days (III) Intragastric injection	(I) Sprague-Dawley rats (II) 3 months (III) Male	Both doses of astaxanthin decreased cerebral infarct volume, oxidative stress, and apoptosis and increased SOD levels and Nrf2 and HO-1 gene expressions.
Ji et al. (2017)	Traumatic brain injury (Weight drop model)	(I) 25 or 75 mg/kg/day (II) 6 days (III) Oral gavage	(I) ICR mice (II) N/A (III) Male	Astaxanthin administration improved sensorimotor coordination problems and spatial and non-spatial memory impairment. It also increased the levels of plasticity-related parameters such as BDNF, GAP-43, synapsin, and synaptophysin in the cerebral cortex.
Nai et al. (2018)	Acute cerebral infarction (MCAO model)	(I) 20, 40, and 80 mg/kg/day (II) 7 days (III) Oral gavage	(I) Sprague-Dawley rats (II) 7–8 weeks (III) Male	Astaxanthin decreased neurological deficit score, cerebral edema, and MDA levels, while increasing antioxidant enzyme (catalase, SOD, and GPx) levels and BDNF and NGF expressions.
Wang et al. (2019a)	Focal cerebral infarction (MCAO model)	(I) 30 mg/kg (twice a day) (II) 28 days (III) Oral gavage	(I) C57BL/6 mice (II) 8–12 weeks (III) Male	Astaxanthin stimulated GAP-43 expression and axonal regeneration in the cerebral cortex and promoted the recovery of motor function in the chronic phase after ischemic infarction.
Wang et al. (2019b)	Subarachnoid hemorrhage (Pre-chiasmatic cistern blood injection model)	(I) 75 mg/kg (II) Single gavage (III) Oral gavage	(I) Sprague-Dawley rats (II) N/A (III) Male	Astaxanthin increased mitochondrial membrane potential, decreased Bax/Bcl-2 ratio and caspase-3 activity, inhibited cytochrome C release, and partially improved cerebral expression of synaptic proteins and neurotrophins in the prefrontal cortex. Thus, it alleviated early brain damage due to subarachnoid hemorrhage by improving neuronal survival.
Zhang et al. (2019)	Subarachnoid hemorrhage (Pre-chiasmatic cistern blood injection model)	(I) 20 μL, 0.1 mM (II) Single injection (III) Ventricular injection	(I) Sprague-Dawley rats and TLR4 KO mice (II) N/A (III) Male	Astaxanthin treatment after subarachnoid hemorrhage reduced the proinflammatory response, inhibited the TLR4 neural pathway, and increased SIRT1 expression. It also reduced brain edema and apoptosis and improved neurological function.
Yang et al. (2021)	Acute cerebral infarction (MCAO model)	(I) 100 mg/kg/day (II) 3 days (III) Oral gavage	(I) Sprague-Dawley rats (II) 6–8 weeks (III) N/A	Astaxanthin pretreatment improved neurological function and reduced inflammation, oxidative stress, cerebral infarct volume, brain edema, apoptosis, and cerebral pathological damage.
Qian et al. (2021)	Subarachnoid hemorrhage (Subarachnoid space blood injection model)	(I) 100 mg/kg (II) Single injection	(I) Specific-pathogen-free mice (II) 8–10 weeks	Astaxanthin treatment inhibited neuroinflammation (decreased IL-6, IL-17 and TNF-α levels and increased IL-10 levels) and apoptosis (decreased Bax levels and increased BcL-2 levels) and decreased NOX2 levels associated with thrombosis.

(*continued on next page*)

Table 7 (*continued*)

Reference	Model	Intervention	Animals	Key results
		(I) Dose (II) Duration (III) Administration	(I) Genus (II) Age (III) Gender	
		(III) Lateral ventricular injection	(III) Male	
Taheri et al. (2022)	Cerebral ischemia/reperfusion (MCAO model)	(I) 25, 45, and 65 mg/kg (II) Single injection (III) Intraperitoneal injection	(I) Wistar rats (II) 12 and 14 weeks (III) Male	Astaxanthin administration dose-dependently decreased stroke volume, neurological deficit score, and lipid peroxidation. All doses increased GPx activity and relative gene expression of catalase, SOD, and GPx.
Huo et al. (2022)	Cerebral Ischemia/Reperfusion (MCAO Model)	(I) 10 mg/kg/day (II) 7 days (III) Subcutaneous injection	(I) Sprague-Dawley rats (II) N/A (III) Male	Astaxanthin reduced neurological severity scores and decreased brain IL-1β, IL-6, and TNF-α levels.
Park et al. (2022)	Transient ischemia (BCCAO model)	(I) 100 mg/kg/day (II) 3 days (III) Intraperitoneal injection	(I) Gerbils (*Meriones unguiculatus*) (II) 6 months (III) Male	Astaxanthin treatment reduced ischemia-induced DNA damage and lipid peroxidation and prevented SOD1 and SOD2 expression decreases in pyramidal cells in CA1 and CA3.
Yeğin et al. (2023)	Cerebral ischemia/reperfusion (BCCAO model)	(I) 25 and 75 mg/kg (II) Single injection (III) Intraperitoneal injection	(I) Wistar rats (II) N/A (III) Male	Astaxanthin increased the levels of antioxidant enzymes (SOD and CAT) and decreased the levels of MDA, and thus exerting neuroprotective effect against brain damage.

MCAO, Middle cerebral artery occlusion; **BCCAO,** Bilateral common carotid artery occlusion; **N/A,** Not available.

to axons and blood vessels with necrotic cell death as a result of force applied directly to the spinal cord (Rowland et al., 2008). The secondary phase consists of a series of molecular and cellular processes such as mitochondrial dysfunction, demyelination, and glial scar formation, as well as inflammation leading to cell death or ischemia (Masoudi et al., 2017, 2021). The inflammatory response begins immediately after spinal cord trauma and peaks within a few days (Hayta and Elden, 2018). Subsequently, the blood-brain barrier is disrupted and both glial and neuronal apoptosis increase (Fakhri et al., 2018). Post-traumatic reperfusion and increased free radicals may exacerbate the secondary damage (Zhang et al., 2012). As a matter of fact, it is known that the lipids of the spinal cord are easily destroyed by free radicals (Hall et al., 2016). These two phases form the basis of sensorimotor dysfunction that can last for years (Fakhri et al., 2018). There is no pharmacological method to treat spinal cord injury in the primary phase. Neuroprotective and regenerative therapeutics that work to reduce secondary damage are rarely used (Nagoshi and Okano, 2017). Therefore, novel therapies targeting the main mechanisms are of great importance. Antioxidant therapy shows promise in promoting functional recovery (Bastani et al., 2012).

The therapeutic effects of astaxanthin, which stands out among natural antioxidants, in cases of spinal cord injury have recently been the subject of many studies. Positive findings regarding the therapeutic effects of astaxanthin have been reported in animal experiments. The therapeutic effects of astaxanthin on spinal cord injury include attenuating oxidative stress and reducing pathological tissue damage, mechanical and thermal pain, spinal cord edema, and apoptosis. Most importantly, it has been shown to improve motor function (Table 8). The first experimental study examining the effect of astaxanthin treatment on spinal cord injury was conducted by (Masoudi et al., 2017). A single dose of astaxanthin (10 μL, 0.2 mM) administered after the application of a weight-drop model (using a 10-g rod) improved locomotor activity, decreased Bax and cleaved caspase-3 expression, reduced pathological tissue damage, and increased Bcl-2 expression, myelinated white matter volume, and motor neuron number. Fakhri et al. (2018) reported that single-dose (10 μl, 0.2 mM) astaxanthin treatment 30 min after spinal cord injury induced by clip compression inhibited the glutamatergic phosphorylated p38 mitogen-activated protein kinase (p-p38 MAPK) signaling pathway and reduced TNF-α expression, thus protecting white matter and motor neurons. These researchers also showed that astaxanthin administered by the same method reduced mechanical and thermal pain and increased the volume of myelinated white matter and the number of motor neurons in the spinal cord. They reported that astaxanthin treatment decreased ERK1/2 activation and increased AKT activation (Fakhri et al., 2019). Fu et al. (2020) administered astaxanthin to rats at a dose of 25 mg/kg for 14 days before abdominal aorta occlusion to investigate the protective effects of astaxanthin on spinal cord injury. They found that astaxanthin pretreatment improved hindlimb motor function, increased SOD levels and GSH activity, and alleviated mitochondrial swelling in the spinal cord, and reduced neuronal apoptosis, MDA, and xanthine oxidase (XO) levels. Li et al. (2021) induced spinal cord injury in rats with the modified Allen method and examined the effects of astaxanthin given at a dose of 75 mg/kg twice daily. Astaxanthin treatment improved MDA and SOD levels examined 24 h after spinal cord injury. The apoptosis index, calculated at 6, 24, and 48 h after spinal cord injury and spinal cord tissue edema, examined at 48 h, both decreased as a result of astaxanthin treatment. It was also found that motor function partially improved. In a different study by Masoudi et al. (2021), it was shown that a single dose of astaxanthin treatment (10 μL, 0.2 mM) 30 min after spinal cord injury decreased IL-1β, IL-6, TNF-α, and COX-2 expressions and MDA levels; increased catalase, SOD, and GSH-Px activities; and prevented loss of myelinated white matter and motor neurons in the spinal cord. Abbaszadeh et al. (2022) investigated the effects of a single dose of astaxanthin (10 μL, 0.005 mg/kg) given 30 min after spinal cord injury induced by clip compression on motor function, autophagy, and neuronal apoptosis. They found that astaxanthin administration improved motor function, decreased MDA levels and the Bax/Bcl-2 ratio, and increased SOD and GPx activity, total antioxidant capacity, and Beclin-1 and LC3B expressions in the spinal cord. In another study, they stated that the same dose of astaxanthin administered by the same method preserved blood-spinal cord barrier integrity, supported motor function, improved spinal tissue edema, and decreased the expression levels of high mobility group box 1 (HMGB1), TLR4, NF-κB, MMP-9, and aquaporin-4 (AQP-4) (Abbaszadeh et al., 2023).

4. Conclusion and future perspectives

Due to the increasing interest and awareness in preventive health behaviors, the “healthy living industry” has replaced the “disease treatment industry.” This has led to an increasing demand for nutraceuticals based on bioactive components. The marine environment represents a massive resource for the identification of previously undiscovered bioactive components. One of the marine-derived bioactive compounds whose health effects are recognized by the scientific world is astaxanthin. Well-controlled studies based on *in vitro* and *in vivo* models have reported that astaxanthin can effectively cross the blood-brain barrier and exhibits antioxidant, anti-inflammatory, and anti-apoptotic

Table 8
Summary of *in vivo* studies evaluating the effect of astaxanthin on spinal cord injury/ischemia-reperfusion.

Reference	Model	Intervention (I) Dose (II) Duration (III) Administration	Animals (I) Genus (II) Age (III) Gender	Key results
Masoudi et al. (2017)	SCI (Weight drop model: a 10-g rod was released onto the exposed spinal cord)	(I) 10 μL, 0.2 mM (II) Single injection (III) Transcutaneous intrathecal injection	(I) Wistar rats (II) 2–3 months (III) Male	Astaxanthin treatment improved locomotor activity, decreased Bax and cleaved caspase-3 expression, increased Bcl-2 expression, myelinated white matter volume, and motor neuron number, and thus reduced pathological tissue damage.
Fakhri et al. (2018)	SCI (Clip compression model)	(I) 10 μL, 0.2 mM (II) Single injection (III) Transcutaneous intrathecal injection	(I) Wistar rats (II) N/A (III) Male	Astaxanthin treatment inhibited the glutamatergic p-p38 MAPK signaling pathway and reduced TNF-α expression, thus protecting white matter and motor neurons.
Fakhri et al. (2019)	SCI (Clip compression model)	(I) 10 μL, 0.2 mM (II) Single injection (III) Transcutaneous intrathecal injection	(I) Wistar rats (II) 2–3 months (III) Male	Astaxanthin treatment reduced mechanical and thermal pain and increased the volume of myelinated white matter and the number of motor neurons in the spinal cord. It also decreased ERK1/2 activation and increased AKT activation.
Fu et al. (2020)	SCII (Abdominal aorta occlusion model)	(I) 25 mg/kg/day (II) 14 days (III) Transcutaneous intrathecal injection	(I) Sprague-Dawley rats (II) 6–8 weeks (III) Male	Astaxanthin pretreatment improved hindlimb motor function, reduced neuronal apoptosis and oxidative stress (decreased MDA and XO levels and increased SOD levels and GSH activity), and attenuated mitochondrial swelling in the spinal cord.
Li et al. (2021)	SCI (Modified Allen method-induced model)	(I) 75 mg/kg/day (II) Twice per day after the operation (III) Intragastric injection	(I) Sprague-Dawley rats (II) N/A (III) Male and female	Astaxanthin treatment improved MDA and SOD levels examined 24 h after spinal cord injury. The treatment also reduced the apoptosis index values examined at 6, 24, and 48 h after spinal cord injury and spinal cord tissue edema examined at 48 h.
Masoudi et al. (2021)	SCI (Contusion trauma-induced model)	(I) 10 μL, 0.2 mM (II) Single injection (III) Transcutaneous intrathecal injection	(I) Wistar rats (II) 2–3 months (III) Male	Astaxanthin attenuated spinal cord tissue damage through antioxidant (decreased MDA levels and increased catalase, SOD, and GSH-Px activity) and anti-inflammatory (decreased IL-1β, IL-6, and TNF-α expressions) effects. It also prevented loss of myelinated white matter and motor neurons.
Abbaszadeh et al. (2022)	SCI (Clip compression model)	(I) 10 μL, 0.005 mg/kg (II) Single injection (III) Transcutaneous intrathecal injection	(I) Wistar rats (II) N/A (III) Male	Astaxanthin administration improved motor function, decreased MDA levels and Bax/Bcl-2 ratio, increased SOD and GPx activity, total antioxidant capacity, and Beclin-1 and LC3B expressions in the spinal cord.
Abbaszadeh et al. (2023)	SCI (Clip compression model)	(I) 10 μL, 0.005 mg/kg (II) Single injection (III) Transcutaneous intrathecal injection	(I) Wistar rats (II) N/A (III) Male	Astaxanthin reduced inflammatory response and edema in the spinal tissue and improved motor function. These effects were associated with the prevention of astrocyte activation, inhibition of the HMGB1/TLR4/NF-κB pathway, maintaining the integrity of the BSCB, and downregulation of AQP4 and MMP-9 expressions.

SCI, Spinal cord injury; **SCII,** Spinal cord ischemia/reperfusion; **BSCB,** Blood-spinal cord barrier, **N/A,** Not available.

properties through multiple mechanisms. It also exerts effects against neurodegeneration by supporting autophagic mechanisms, blood-brain and blood-spinal cord barrier integrity, neurogenesis, and neuroplasticity. Improvement of mitochondrial abnormalities is also among its highlighted properties. Because of all these activities, astaxanthin appears to be an excellent candidate for further evaluation of its neurotherapeutic effects. It is not far-fetched that natural astaxanthin supplementation may represent a co-adjuvant therapy in the management of neurodegenerative diseases. However, researchers still need to determine whether all these positive health effects are due to the astaxanthin molecule itself or its metabolites. In addition, although limited evidence favors the Z isomer in terms of health benefits, more comprehensive studies comparing the neuroprotective and neurotherapeutic effects of different astaxanthin isomers would also contribute to the literature. Finally, the potential mechanisms of action reported for astaxanthin treatment are based on *in vitro* and animal studies. Well-designed human studies are needed to evaluate the clinical benefits of astaxanthin in neurodegenerative diseases.

CRediT authorship contribution statement

Emre Adıgüzel: Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Taha Gökmen Ülger:** Writing – original draft, Visualization, Validation, Software, Resources, Formal analysis, Data curation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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