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Review

"Therapeutic uses of natural astaxanthin: An evidence-based review focused on human clinical trials"

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ABSTRACT

Astaxanthin is a natural C40 carotenoid with numerous reported biological functions, most of them associated with its antioxidant and anti-inflammatory activity, standing out from other antioxidants as it has shown the highest oxygen radical absorbance capacity (ORAC), 100–500 times higher than α-tocopherol and a 10 times higher free radical inhibitory activity than related antioxidants (α-tocopherol, α-carotene, β -carotene, lutein and lycopene). *In vitro* and in vivo studies have associated astaxanthin's unique molecular features with several health benefits, including neuroprotective, cardioprotective and antitumoral properties, suggesting its therapeutic potential for the prevention or co-treatment of dementia, Alzheimer, Parkinson, cardiovascular diseases and cancer. Benefits on skin and eye health promotion have also been reported, highlighting its potential for the prevention of skin *photo-aging* and the treatment of eye diseases like glaucoma, cataracts and uveitis. In this review, we summarize and discuss the currently available evidence on astaxanthin benefits, with a particular focus on human clinical trials, including a brief description of the potential mechanisms of action responsible for its biological activities.

1. Introduction

Antioxidants can be defined as molecules that, at low concentrations, delay or prevent oxidation, acting at biological membranes, or at intracellular levels, therefore protecting the cells of different organs and diverse biological systems [11,60]. Among natural antioxidants, carotenoids and their derivatives stand out as a broad group of molecules that are naturally produced by plants and other photosynthetic organisms. These molecules are capable of protecting cells from oxidative processes mediated either by light, free radical-mediated peroxidation, or singlet oxygen [49]. Given these properties, the effects of carotenoids on health and their cosmetic benefits have been under investigation for a long time [73]. Among them, astaxanthin, a red C40 molecule, is one of the most abundant aquatic carotenoids, standing out among its chemical family as it has been shown to have the highest oxygen radical absorbance capacity, with a 100–500 times more antioxidant capacity than α-tocopherol (Vitamin E), a well-known and commonly used antioxidant [42,63]. Several sources of natural astaxanthin have been reported, including the microalgae *Haematococcus pluvialis* (recently renamed as *H. lacustris* according to the taxonomy study carried by [61]), *Chlorella vulgaris, Chlorella zoofingiensis* and *Chlorococcum* sp. It is also naturally synthesized by the red yeast *Phaffia rhodozyma* [28]. Among these, *H. pluvialis* is currently the only natural source of astaxanthin approved for human consumption [4,75]. Astaxanthin can also be included indirectly in our diet by consuming crustaceans (e.g., copepods, shrimp, and krill) and Salmonidae (e.g., salmon, rainbow trout) species, whose diets include natural sources of astaxanthin.

The astaxanthin molecule has two asymmetric carbon atoms at positions 3 and 3' (Fig. 1). Consequently, there are different possible optical isomers or enantiomers: 3S, 3'S; 3R, 3'R; and 3R, 3'S. In nature, isomers with a chirality 3S, 3'S, or 3R, 3'R are the most abundant, among which, the former has the highest reported antioxidant activity [4,63,97]. Synthetic astaxanthin consists in a combination of 3R,3'R; 3R, 3'S; and 3R,3'R isomers (1:2:1) [46]. Astaxanthin contains

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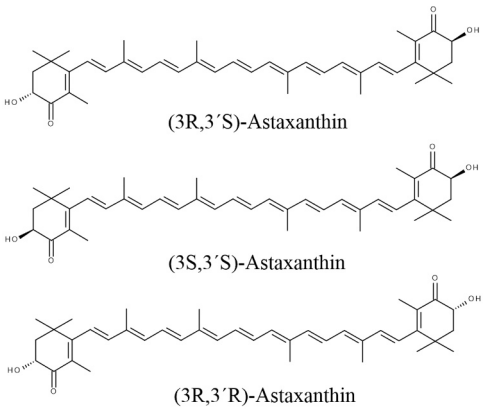

Fig. 1. Stereoisomers of astaxanthin (1-column fitting).

conjugated double bonds, hydroxyl, and keto groups, showing both lipophilic and hydrophilic properties [28]. The conjugated double bonds at its center are responsible for its red color and, most important, for its high antioxidant capacity, as it donates the electrons that react with free radicals to convert them into more stable products, blocking free radical chain reactions [4]. Astaxanthin can also trap free radicals in its terminal ring moiety, in which the hydrogen atom at the C3 methine has been suggested to be a radical trapping site [92]. As astaxanthin shows both lipophilic and hydrophilic properties, this molecule is exposed to both the inside and outside of the cell, where it can scavenge radicals from the surface of the cell and at the interior of the phospholipid membrane (Fig. 2). This feature makes astaxanthin unique when compared to other antioxidants, such as β-carotene or vitamin C, which can only reside within or outside the lipid bilayer membrane, respectively [92]. Indeed, studies have demonstrated that astaxanthin shows the highest antioxidant activity when compared to related carotenoids, being 10 times stronger. Miki [50] studied the scavenger effect of astaxanthin and related carotenoids (zeaxanthin, lutein, tunaxanthin, canthaxanthin and β-carotene) against free radicals, using the thiobarbituric acid reactive substances (TBARS) assay with α-tocopherol as control. The results showed that astaxanthin has the highest scavenger effect, with an ED_{50} of aproximately 200 nM, whereas other carotenoid samples were in the range of 200–1000 nM. *In vivo* assays carried in the same study also demonstrated that astaxanthin shows the lowest ED_{50} values (2 μM) when assessing its inhibitory activity against the action of free radicals on rat blood cells and mithochondria. More specific fluorometric assays, based on BODIPY fluorescent probes that are susceptible to oxidation by peroxyl radicals, have also demonstrated that astaxanthin shows the highest relative antioxidant activity (1.3 ± 0.2) when compared to the antioxidant Trolox (1.0) and the carotenoids α-tocopherol (0.9), α-carotene (0.5), β -carotene (0.2), lutein (0.4) and lycopene (0.4) [59, 60].

Given its unique features, astaxanthin has been widely studied in the last years, both in animal and human models, showing neuroprotective, cardioprotective and antitumoral properties, together with promising results on skin and eye health promotion, suggesting its therapeutic potential for the prevention or co-treatment of diseases such as dementia, Alzheimer, Parkinson, cardiovascular diseases, cancer and glaucoma, among others. Here, we provide an updated view of natural astaxanthin's benefits and its therapeutic uses, focusing on those that have shown evidence or promising results in human clinical trials.

2. Pharmacokinetics of astaxanthin

Like all carotenoids, astaxanthin is absorbed by the organisms alongside fatty acids via passive diffusion into the intestinal epithelium. Briefly, astaxanthin mixes with bile acid after ingestion and forms micelles in the intestine. The micelles containing astaxanthin are partially absorbed by intestinal mucosal cells, which are incorporated into chylomicrons to be delivered to the liver. Then, astaxanthin is assimilated with lipoproteins and transported to different tissues. Importantly, astaxanthin has been reported to preserve the integrity of cell membranes by inserting itself in the lipid bilayers, altogether protecting the redox state and functional integrity of the mitochondria. Once degraded, carotenoids are stored in the liver and re-secreted, either as very low-density lipoproteins (VLDL), low density lipoproteins (LDL), and high-density lipoproteins (HDL), eventually being transported to the tissues via circulation [98,99].

3. Biological activities of astaxanthin

Different studies have shown a wide range of potential mechanisms through which astaxanthin might exert its benefits, including photoprotective, antioxidant, anti-inflammatory, and anti-apoptosis effects, which act at different levels, including benefits to the skin, cardiovascular system, and eyes. In addition, several studies have demonstrated its neuroprotective capacity and antitumoral activity (Fig. 3). In the following sub-sections, we review the latest and most relevant studies regarding astaxanthin's therapeutic uses, focusing on those that have shown promising results in human trials. A summary of these and other promising clinical trials are also described in detail in Tables 1–6.

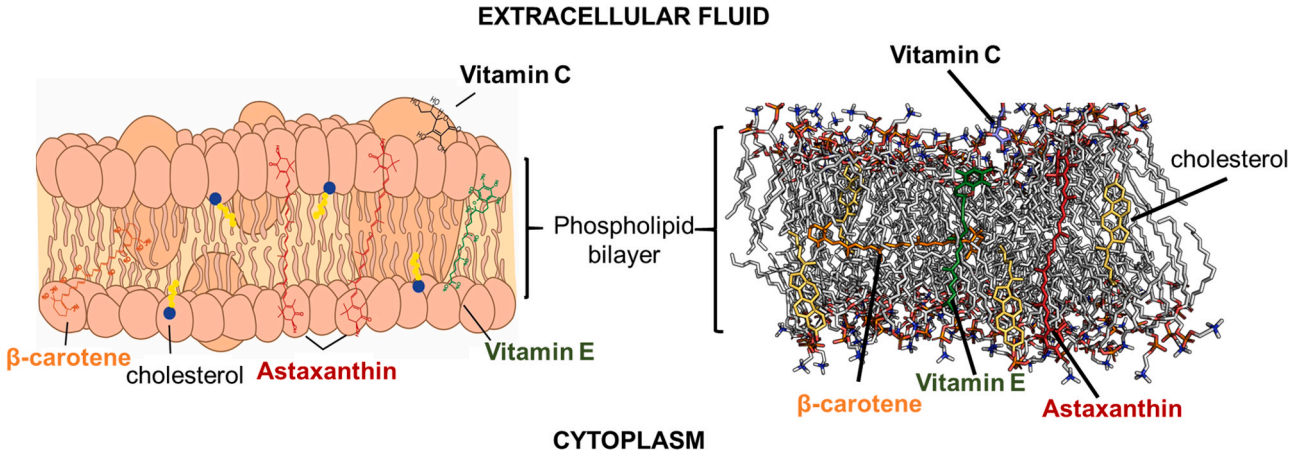

Fig. 2. Schematic (left) and tridimensional (right) view of the astaxanthin molecule and other common antioxidants location at the cell membrane. (Color/2-column fitting).

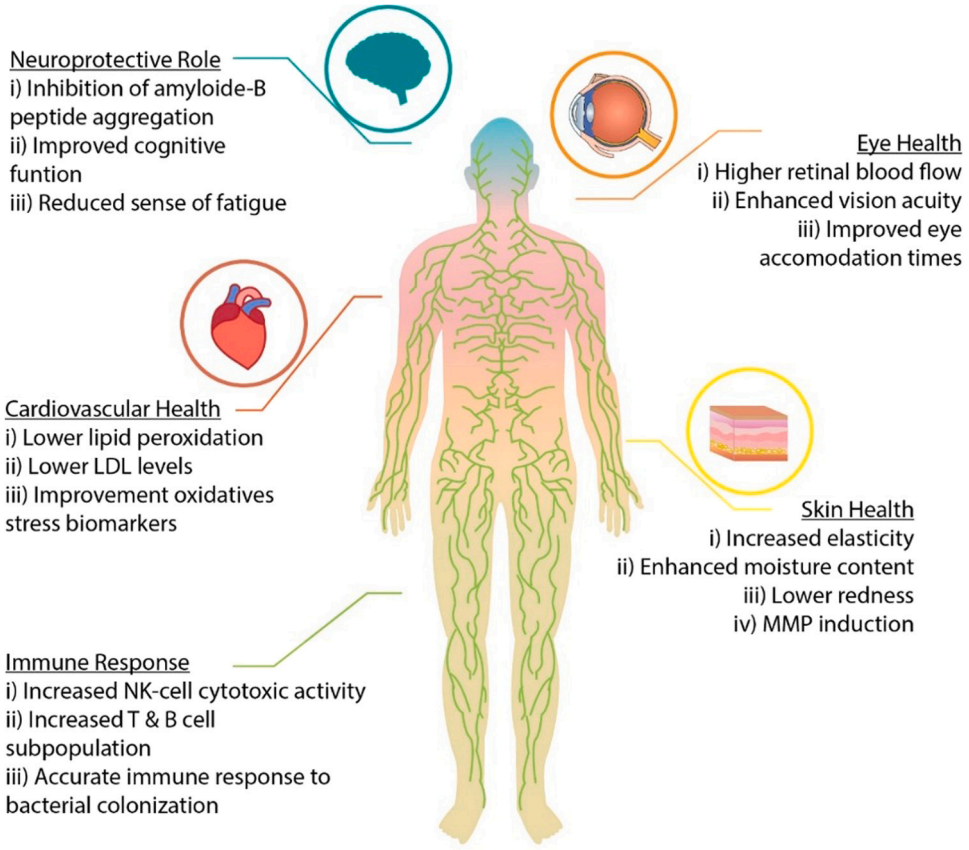

Fig. 3. Summary of therapeutic benefits of astaxanthin intake as reported in different clinical trials (Color/1-column fitting).

3.1. Skin health

Skin is the primary barrier through which our organism interacts with the external environment. Therefore, it is exposed to direct oxidative stress, including ultraviolet (UV) radiation [70,82]. During aging, skin health is mostly affected by oxidative stress associated with the generation of reactive oxygen species (ROS) via oxidative metabolism and UV light exposure, which leads to accelerated extrinsic skin aging (Fig. 4), also known as "photo-aging" [68]. Several oxidant events are associated with skin aging, including DNA damage, reduced production of antioxidants, inflammatory responses, and the presence of matrix metalloproteinases (MMPs). Besides its antioxidant properties, the main mechanisms through which astaxanthin protects skin include its anti-inflammatory properties, immune-enhancing effects, DNA repair, and suppression of skin damage caused by MMP induction. MMPs are zinc-containing endopeptidases that degrade various components of extracellular matrix (ECM) proteins, including collagen and elastin [13,19,70]. Alterations in the ECM have been associated with skin wrinkling and, more important, its degradation contributes to photocarcinogenesis, which is an initial step towards tumor cell invasion, as MMPs degrade fibrillary collagens present in the basement membrane and surrounding stroma. Additionally, MMPs are involved in angiogenesis, promoting cancer cell growth and migration [70]. Yoon et al. [93] conducted a 12-week, randomized, double-blind placebo--controlled study, assessing the effect of dietary astaxanthin and collagen on photoaged skin by administering astaxanthin capsules (2 mg) in combination with hydrolyzed collagen tablets to 44 healthy female volunteers. After UV-irradiation, molecular analysis showed a significant reduction in the expression of genes *mmp-1* (collagenase) and *mmp-12* (elastase) in the supplemented group, being suppressed by 68% ($p = 0.027$) and 77% ($p = 0.050$), respectively. These results agree with the findings reported by Tominaga et al. [85], where MMP1 levels were measured in fibroblasts after incubation with media derived from keratinocytes treated with 0, 1, 5 or 10 μM astaxanthin before and after irradiation with UVB, reporting that MMP-1 levels significantly decreased ($p < 0.01$) in a dose-dependent manner in the presence of medium derived from astaxanthin-treated keratinocytes.

Most human clinical trials regarding skin health focus on cosmetic parameters, such as skin wrinkles, age spots size, elasticity, skin texture, moisture content, corneocyte condition reduction, and sebum oil content. The aforementioned study conducted by Yoon et al. [93] also reported a significant improvement in skin gross elasticity (R2,0.0252 vs. −0.0294, $p = 0.035$), net elasticity (R5, 0.0602 vs. −0.0195, $p = 0.020$) and biological elasticity (R7, 0.0222 vs. −00185, $p = 0.012$) in the supplemented vs. placebo groups, respectively. Both results suggest that dietary astaxanthin combined with collagen hydrolysate can improve the elasticity and barrier integrity in photo-aged human facial skin. A 16-week clinical study conducted by Tominaga et al. [85], with 65 healthy female participants orally administered either a 6 mg or 12 mg dose of astaxanthin or a placebo, demonstrated that skin moisture displayed significant deterioration in the placebo group (204.9 ± 54.2 μS) compared with that at week 0 (264.7 ± 100.3 μS), while no significant deteriorations were observed in the astaxanthin-treated groups. A stratified wrinkle analysis also showed that the mean depth of the deepest wrinkle, maximum depth of the deepest wrinkle and mean depth of all wrinkles significantly ($p < 0.01$) worsened in the placebo group at week 16 (68.6 ± 23.0, 172.0 ± 53.6 and 59.9 ± 19.8 μm, respectively) compared with those at week 0 (43.6 ± 11.6, 108.6 ± 29.2 and 42.9 ± 13.7 μm, respectively), while no significant worsening s was observed in the astaxanthin-treated group. Similar results have been reported, observing significant improvements ($p < 0.01$) in wrinkle depth parameters in an open-label non-controlled study involving 30 healthy female subjects for 8 weeks, after oral supplementation with oral (6 mg/day) and topical (2 mL of 78.9 μM solution/day) astaxanthin

Table 1
Summary of human clinical trials targeting skin health with natural astaxanthin.

Tested Parameters	Experiment design	N and Health state	ATX dosage	Length of study (weeks)	Results	Reference
Minimal erythema dose (MED) and analyzed UV-induced changes of moisture and transepidermal water loss (TEWL). Subjective skin conditions were assessed by the visual analog scale	randomized, double-blind, placebo-controlled trial	23 healthy volunteers	4 mg daily	10	Astaxanthin group showed increased MED compared with placebo. In addition, the astaxanthin group had a reduced loss of skin moisture in the irradiated area compared with placebo. Subjective skin conditions for "improvement of rough skin" and "texture" in non-irradiated areas were significantly improved by astaxanthin	[34]
Skin moisture	Open-Label	11 females	0.7 mg/g Atx containing cream, applied twice a day	3	Reduced skin dryness, with an increase in skin moisture.	[96]
Crow's feet wrinkle, elasticity, transepidermal water loss (TEWL) were measured	Randomized double-blind and Placebo controlled	36 Healthy males	6 mg daily	6	Significant improvements were observed in wrinkle and elasticity of crow's feet and TWEL at cheek	[86]
RSSC samples were collected from the surface of the facial skin, plasma levels of malondialdehyde were measured, which allowed assessing systemic oxidative stress	Open-label	41 Healthy, over 40 y/o	4 mg Daily	4	Plasma malondialdehyde consistently decreased during astaxanthin consumption, they found significantly decreased levels of corneocyte desquamation and microbial presence.	[8]
Wrinkle topography measurements were taken,skin elasticity and size of age spots quantified,skin topography measurements made, and cellsize in the corneocyte measured	Open-label and non- controlled	30 Healthy females	6 mg + 2 mL of 78.9 uM topical solution	8	Significant improvements on all parameters measured were observed, except moisture content of corneocyte layer in the cheek, were no significant difference was shown.	[86]
Wrinkle parameters, skin moisture content, interleukin-1α levels in the stratum corneum were measured	Randomized double-blind and Placebo controlled	65 Healthy females	6,12 mg daily	16	Parameters did not significantly changed, but in placebo group, parameters dramatically deteriorated.	[85]
Dermatologist assesment	Randomized double-blind and Placebo controlled	28 Healthy, middle aged women	4 mg daily	6	Moisture content and elasticity improved significantly.	[92]
The elasticity and hydration properties of facial skin were evaluated	Randomized double-blind and Placebo controlled	44 Healthy females	2 mg daily	12	Improvement on skin elasticity parameters and the stratum corneum barrier in both groups was significantly improved,	[93]
Wrinkle topography measurements were taken,skin elasticity and size of age spots quantified,skin topography measurements made, and cellsize in the corneocyte measured	Open-Label	28,30,29,30,30	6 mg daily	8	Spots sized reduced, skin texture improved. Found improvements with acne, sebum production and pregnancy skin-changes	[84]

Table 2
Summary of human clinical trials targeting eye health with natural astaxanthin.

Tested Parameters	Experiment design	N and Health state	ATX dosage	Length of study (weeks)	Results	Reference
Accommodation, critical nicker fusion (CFF) and pattern visual evoked potential (PVEP) test were implemented.	Double masked study	26 Visual display terminal workers	5 mg daily	4	Accommodation amplitude was significantly larger than at day 0. CFF and PVEP values did not change after supplementation	[56]
Hemodynamics of the choroidal circulation were measured with LSFG. SBR, a quantitative index for relative blood flow velocity was calculated at baseline, 2, and 4 weeks.	Randomized double-blind and Placebo controlled	20 healthy volunteers	12 mg daily (6 mg twice a day)	4	Significant increase of the macular SBR	[72]
Static and kinetic visual acuity, depth perception and critical flicker fusion (CFF) were measured	Randomised, double-blind, placebo-controlled	18 Healthy males	6 mg daily	4	a significant improvement in both deep vision and CFF was observed in the treated group, when compared to the control group	[74]
Retinal capillary blood flow, blood pressure, blood cell counts, fasting plasma glucose level, and intraocular pressure were measured	Randomized double-blind and Placebo controlled	36 healthy volunteers	6 mg daily	4	Possitive effect on retinal blood flow	[57]

[86]. More studies assessing similar parameters are reviewed in Table 1. Parameters such as skin redness or erythema have also been reported to decrease by 60%, 98 h after UV-B exposure in healthy male subjects (n = 7) treated with topical astaxanthin [91]. In 2018, Ito, Seki, and Ueda, studied the protective role of astaxanthin against UV skin deterioration on 23 healthy volunteers. The authors measured minimal erythema dose (MED), after 4 mg/day supplementation on a ten-week period, reporting that the astaxanthin group showed a significant

Table 3
Summary of human clinical trials targeting cardiovascular health with natural astaxanthin.

Tested Parameters	Experiment design	N and Health state	ATX dosage	Length of study (weeks)	Results	Reference
Total cholesterol, triglycerides, high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol, apolipoprotein A1 (ApoA1), and apolipoprotein B (ApoB) were measured. Also, Malondialdehyde (MDA), isoprostane (ISP), superoxide dismutase (SOD), and total antioxidant capacity (TAC), as oxidative stress biomarkers, were measured	Randomized double-blind and Placebo controlled	27 Body mass index >25.0 kg/m2	20 mg daily	12	LDL cholesterol and ApoB were significantly lower after treatment with astaxanthin. Compared with the placebo group, MDA and ISP were significantly lower, but TAC was significantly higher in the astaxanthin group at 12 weeks	[10]
Malondialdehyde (MDA), isoprostane (ISP), superoxide dismutase (SOD) and total antioxidant capacity (TAC), as oxidative stress biomarkers, were measured	Randomized double-blind and Placebo controlled	23 BMI > 25.0 kg/m2	5, 20 mg daily	3	MDA and ISP were significantly lowered, SOD and TAC levels increased significantly	[10]
Fasting venous blood samples were taken, LDL oxidation lag measured	Open-label	24 healthy volunteers	1.8, 3.6, 14.4 and 21.6 mg daily	2	LDL lag time was longer compared with day 0 after consuming astaxanthin at doses.	[35]
body mass index (BMI) and LDL-cholesterol, triglyceride decreased, while HDL-cholesterol, Serum adiponectin	Randomized placebo-controlled	61 Females and males with mild hyperlipidemia	0, 6, 12 and 18 mg daily	12	Triglyceride decreased, while HDL-cholesterol increased significantly. Serum adiponectin was increased by astaxanthin, and changes of adiponectin correlated positively with HDL-cholesterol changes	[94]
Astaxanthin absorption and safety	Randomized, double blind trial	20 Non-smoking males	8 mg daily (4 mg twice per day)	12	Levels of plasma 12- and 15-hydroxy fatty acids were reduced statistically significantly in the astaxanthin group.	[37]
Astaxanthin and PLOOH levels in the erythrocytes were measured	Randomised, double-blind, placebo-controlled	30 Middle aged and senior	6, 12 mg daily	12	Erythrocyte astaxanthin concentrations were higher. PLOOH levels in plasma and erythrocytes were lower	[62]
A whole blood transit time test was conducted using heparinized blood of the volunteers by a MC-FAN apparatus.	Single-blind method	20 Males	12 mg daily	10 days	Ingestion group showed significantly lower values	[51]

Table 4
Summary of human clinical trials targeting neurological health with natural astaxanthin.

Tested Parameters	Experiment design	N and Health state	ATX dosage	Length of study (weeks)	Results	Reference
the Japanese version of the Central Nervous System Vital Signs (CNSVS) test and the Alzheimer's Disease Assessment Scale-Cog test	Randomized double-blind and Placebo controlled	21 Healthy, with mild cognitive impairment	3 mg daily + 5 mg of sesamin	12	CNSVS test revealed significant improvements in psychomotor speed and processing speed	[33]
Somatometry, haematology, urine screens, and CogHealth and Groton Maze Learning Tes	Randomized double-blind and Placebo controlled	96 Healthy middle aged and elderly	6, 12 mg daily	4	CogHealth battery scores improved in the high-dosage group, Groton Maze Learning Test scores improved earlier	[38]
A Uchida-Kraepelin performance tests was performed, subjects cycled. and answered a Profile of Mood States (POMS) questionnaire, also, biological antioxidant potential (BAP) was measured	randomized, placebo-controlled, parallel-group	39 Fatigued volunteers	12 mg daily + 20 mg of tocotrienol	12	Intent-to-treat analysis revealed that the sense of fatigue after both physical and mental loading was significantly lower in the astaxanthin group than in the control group in Week 8. The change in Friendliness in POMS was significantly higher in the astaxanthin group than in the control group in Week 8. No significant differences were observed in the change rate in the BAP value in Week 12 between the astaxanthin group and control group	[29]
Volunteers performed a visual display terminal task and ergometer task. Subjective fatigue was evaluated daily by the Chalder fatigue questionnaire. Also work efficiency, autonomic nerve activity, levels of an oxidative stress marker (plasma phosphatidylcholine hydroperoxide (PCOOH)) and safety was considered	Randomized, double-blind, placebo-controlled, two-way crossover	24 healthy volunteers	3 mg daily +5 mg of sesamin	4	AS supplementation was associated with significantly improved recovery from mental fatigue. Increased PCOOH levels during mental and physical tasks were attenuated by AS supplementation	[31]

Table 5
Summary of human clinical trials targeting immune response with natural astaxanthin.

Target	Tested Parameters	Experiment design	N and Health state	ATX dosage	Length of study (weeks)	Results	Reference
Immune response	Immune response and tuberculin test performed.	randomized double-blind, placebo-controlled	42 Young, healthy adult females	0, 2, 8 mg daily	8	Astaxanthin decreased a DNA damage biomarker after 4 wk but did not affect lipid peroxidation, Dietary astaxanthin stimulated mitogen-induced lymphoproliferation, increased natural killer cell cytotoxic activity, and increased total T and B cell subpopulations. plasma IFN-γ and IL-6 increased on wk 8 in subjects given 8 mg astaxanthin	[69]
	salivary IgA (sIgA) and oxidative stress status in plasma, along with changes in biochemical parameters and total/differential white cell counts	Randomized double-blind and Placebo controlled	40 Male soccer players	4 mg daily	12	Plasma muscle enzymes levels were reduced significantly. When compared to placebo group,there was a significant blunting of the systemic inflammatory response.	[7]
	IL-4, IL-6, IL-8, IL-10, interferon-γ, CD4, CD8, CD14, CD19, CD25 and CD30	Randomized, placebo controlled	44 *H. Pylori*-positive	40 mg daily	Not informed	a significant decrease in gastric inflammation in H. pylori-positive patients from both groups. There were no significant changes in the density of H. pylori or in any of the	[5]

($p < 0.05$) increase in MED (MED = 5) from baseline compared with the placebo group (MED = 1) after supplementation. Furthermore, a morphological analysis of the residual skin surface components (RSSCs) was Chalyk et al. [8], demonstrating the benefits of astaxanthin ingestion when studying 31 middle-age volunteers. The term RSSCs usually comprises the mixture of substances recovered from the skin surface, such as sebum, sweat, corneocyte debris characteristics, [76]. In this study, Chalyk et al. [8] reported a significant decrease in corneocyte desquamation levels ($p = 0.0075$) and microbial presence ($p = 0.0367$) ($P = 0.0367$), as well as a significant increase in lipid droplet size ($p = 0.0214$), all associated with a skin of younger age.

3.2. Eye health

Oxidative damage has been reported to play an essential role in several ocular diseases. Among these, the most common include age-related macular degeneration [30], cataract [81], uveitis [26], retinopathy of prematurity [64], corneal inflammation [3], and keratitis [2]. Oxidation, as mentioned before, promotes membrane degradation. In the eyes, this might lead to damage or destruction of photoreceptor cells located in the macula, the central area of the retina responsible for visual acuity. Studies have demonstrated that certain carotenoids protect the retina by preventing oxidative damage, therefore, retarding some of the destructive processes of the retina and the retinal pigment epithelium that lead to the degeneration of the macula. Such is the case of the dihydroxy carotenoids lutein and zeaxanthin, present in high densities in the macula [80]. Among other xanthophylls, astaxanthin has also been reported to protect epithelial cells in the human eye from UVB-induced stress [9].

Astaxanthin benefits on eye health have been studied in both animal models and humans, demonstrating positive effects on retinal blood flow, vision acuity, and uveitis, among others [23]. The double-blind, randomized placebo-controlled study conducted by Nagaki et al. [57] assessed the effect of astaxanthin on retinal capillary blood flow in 36 healthy volunteers. Two groups of 18 volunteers each were given either oral astaxanthin (6 mg/day) or a placebo consisting of an identical-looking oral dose, respectively, for four weeks. The astaxanthin supplemented group showed a significantly ($p < 0.01$) higher retinal capillary blood flow in both eyes after supplementation, without lowering intraocular pressure, while it remained unchanged in the placebo group after treatment. These results are especially important, as a circulatory failure in the optic papilla has been associated with glaucoma optic nerve disorders (Anderson and Quigley 1992; [66,67]), suggesting that astaxanthin could be beneficial for its treatment. Other studies have also reported beneficial effects of astaxanthin on blood rheology in human models [51,72]. Specifically, astaxanthin increases choroidal blood flow velocity, as reported by Saito et al. [72], when studying the hemodynamics of the choroidal circulation. This study, with a double-blind, placebo-controlled design was used to examine 20 healthy volunteers after ingestion of astaxanthin (12 mg/day) or placebo capsules for 4 weeks. The results showed that Square Blur Rate (SBR), a quantitative index of relative blood flow velocity, was significantly increased ($P = 0.018$) after astaxanthin ingestion in the supplemented group when compared to pre-ingestion values. In contrast, no SBR differences were detected in the placebo group. Improvement of visual acuity has also been reported. Sawaki et al. [74] studied 18 male volunteers, which were equally divided into two groups. Both groups were supplemented for four weeks with either astaxanthin (6 mg/day) or placebo capsules. Parameters such as static and kinetic visual acuity, depth perception, and critical flicker fusion (CFF) were measured. Depth perception (DP) provides a degree of cubic visual acuity, being indispensable to recognize a located paint and distance in front and rear of a target [74], while CFF levels provide criteria to evaluate the degree of visual fatigue [14]. In this study, a significant improvement ($P = 0,05$) in both deep vision and CFF was observed in the treated group when compared to the control group. However, contradictory results have been

Table 6
Summary of other promising human clinical trials.

Target	Tested Parameters	Experiment design	N and Health state	ATX dosage	Length of study (weeks)	Results	Reference
Fatigue and oxidative damage in muscle	Build up of lactic acid	Randomised, double-blind, placebo-controlled	16 Healthy males	6 mg daily	4	Serum lactic acid concentration at 2 minutes after activity (1,200 m running) of the treated group was significantly lower than that of the control one	[74]
	PON1 activity was assessed (paraoxon and diazoxon), total sulphydryl group content (-SH groups), thiobarbituric acid-reactive substances (TBARS), advanced oxidation protein products and redox balance	Randomized double-blind and Placebo controlled	40 Young soccer players	4 mg daily	12	The significant interaction effect of supplementation and training ($p < 0.05$) on PON1 activity toward paraoxon was observed. The PON1 activity toward diazoxon increased in Asx group after 90 days ($p < 0.01$). SH groups content rose from pre- to post-supplementation period only in Asx group	[102]
	Analysis of thiobarbituric acid-reacting substances (TBARS), advanced oxidation protein products (AOPP), superoxide anion ($O2^{-}$), total antioxidative status (TAS), sulphydril groups (SH), superoxide-dismutase (SOD), serum creatine kinase (CK) and aspartate aminotransferase (AST)	Randomized, double blind trial	32 Elite soccer male players	4 mg daily	12	TAS levels decreased significantly post-exercise only in placebo group, basal SOD activity significantly decreased on both groups by the end of the study. Postexercise CK and AST levels were significantly lower in ATX group. All participants showed a significant decrease in basal CK and AST activities after 90 days.	[103]
Sperm	Semen parameters, reactive oxygen species (ROS), zona-free hamster oocyte test, serum hormones including testosterone, luteinizing hormone (LH), follicle stimulating hormone (FSH) and Inhibin B, and spontaneous or intrauterine insemination (IUI)-induced pregnancies were evaluated	Double blind, randomized trial	30 Male, infertile	16 mg daily	12	ROS and Inhibin B decreased significantly and sperm linear velocity increased, results of the zona-free hamster oocyte test tended to improve, but not reaching statistical significance. The total and per cycle pregnancy rates were higher on ATX group	[104]

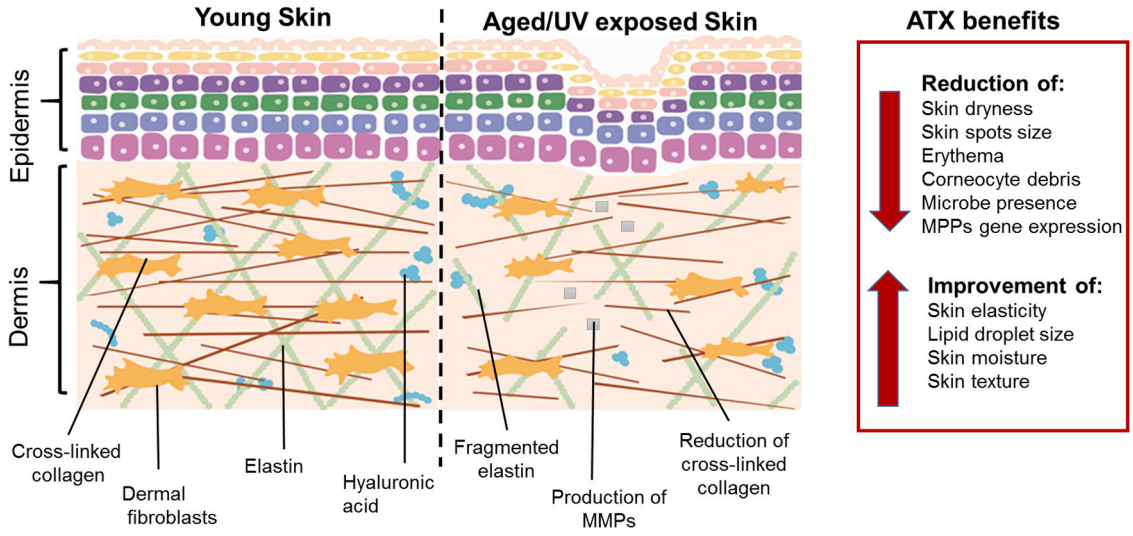

Fig. 4. Aging/UV exposure effects on skin associated to oxidative stress and benefits of astaxanthin intake on skin health evidenced in clinical trials (Color/2-column fitting).

reported by Nagaki et al. [56], when studying the effects of astaxanthin on visual display terminal workers. In this study, no significant differences were found for CFF between a placebo group (n = 13) and a test group (n = 13) after supplementation with astaxanthin (0 mg/day and 5 mg/day, respectively) for four weeks. However, interesting results were found in the same study when assessing eye accommodation, which corresponds to the ability of the eye to change its focus from distant to near objects, and vice versa. After ingestion, a significant improvement ($p < 0.05$) in the amplitude of accommodation was observed in the test group when compared to the placebo group [56].

3.3. Cardiovascular health

Cardiovascular disorders or cardiovascular diseases (CVD) are major illnesses associated with heart and blood vessels, including cerebrovascular disease, coronary heart disease, peripheral artery disease, rheumatic heart disease, congenital heart disease, and heart failure [36]. According to the World Health Organization (WHO), CVD is the leading cause of morbidity and mortality worldwide, projecting it will be the cause of death of 23.3 million people by 2030 [44,6,87]. ROS are responsible for the pathophysiology of various cardiovascular disorders;

for example, oxidative modification of low-density lipoprotein (LDL) has been associated with the pathogenesis of atherosclerosis [16]. ROS are also responsible for the pathophysiology of cardiac hypertrophy, cardiomyopathy, heart failure, ventricular remodeling, ischemia/reperfusion injury, and myocardial infarction [24]. In this context, several dietary antioxidants have been studied, showing positive results for the treatment and prevention of CVD. Such is the case of some polyphenols, carotenoids, ascorbic acid, and vitamin E [36]. Carotenoids have been associated with a potential reduction of cardiovascular risk as they promote lowering of blood pressure, reduction of pro-inflammatory cytokines, and improvement of insulin sensitivity in muscle, liver, and adipose tissues. Specifically, astaxanthin has been the subject of many studies related to CVD treatment and prevention, demonstrating it improves blood lipid profiles [21]. The results of an in vitro study showed that LDL oxidation lag time was significantly prolonged in a dose-dependent manner when adding astaxanthin to a reaction system consisting of LDL and the oxidant V-70. The same study also evaluated LDL oxidation *ex vivo* in blood samples taken from 24 healthy volunteers, separated into five groups that consumed 0, 1.8, 3.6, 14.4, or 21.6 mg of astaxanthin-containing supplements per day for 14 days. LDL oxidation lag time increased in the groups supplemented with astaxanthin (3.6 and 14.4 mg/day, $p < 0.05$; 21.6 mg/day, $p < 0.01$), with no significant differences registered in the control group [35]. Even though experimental investigations have been carried in a range of species, only a few human clinical trials have been conducted in the last two decades to study the effects of astaxanthin in cardiovascular health. In 2007, Karppi et al. evaluated the effects of a three-month astaxanthin supplementation (4 mg twice per day) on lipid peroxidation, which is known to play an important role in the etiology of many pathological conditions, including atherosclerosis. The study was a randomized, double-blind trial based on comparing two parallel identically sized groups (astaxanthin and placebo group), each one consisting of 20 healthy non-smoking men. Plasma levels of 12- and 15-hydroxy fatty acids were reduced significantly ($p = 0.048$ and $p = 0.047$) in the astaxanthin-supplemented groups, suggesting that supplementation with astaxanthin may decrease in vivo oxidation of fatty acids in healthy men. In 2010, the positive effects of astaxanthin on serum HDL-cholesterol were reported for the first time in a randomized, placebo-controlled human study [94]. In this study, placebo-controlled astaxanthin administration at doses of 0, 6, 12, 18 mg/day for 12 weeks were randomly allocated to 61 (41 men and 20 women) non-obese subjects aged 25–60 years with mild hyperlipidemia, reporting a significant increase ($p = 0.0089$) in HDL-cholesterol and adiponectin in the supplemented group. In addition, a significant reduction ($p < 0.01$) in triglyceride levels was reported in the same group. Lipid profiles and oxidative stress were also studied in 27 overweight subjects (20–55 years) before and after astaxanthin (20 mg/day) ingestion for 12 weeks in a randomized, double-blind, placebo-controlled trial [10]. LDL cholesterol ($p < 0.05$) and apolipoprotein B ($p < 0.01$) were significantly lower after treatment with astaxanthin, whereas none of the lipid profiles was changed in the placebo group. Also, oxidative stress biomarkers, including malondialdehyde, isoprostane, superoxide dismutase, and total antioxidant capacity, were improved in the treatment group.

3.4. Neuroprotective properties of astaxanthin

Our brain is especially vulnerable to the effects of oxidative stress, considering its high oxygen demand, its abundance of peroxidation-susceptible lipid cells, and a limited cellular regeneration capacity [32,40]. Neurodegenerative diseases are a heterogeneous group of disorders characterized by a progressive, selective loss of anatomically or physiologically related neuronal systems. The most common are Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, and Huntington's disease [45]. It is recognized that aging is the leading risk factor contributing to these diseases, suggesting that cumulative oxidative stress plays a significant role, associated explicitly with cellular damage, impairment of the DNA repair system, mitochondrial mutations, and mitochondrial dysfunction [22,40,45]. Considering the role of oxidative stress in neuronal disorders, there is a growing interest in antioxidant therapies. Several clinical trials have been conducted in order to study the neuroprotective properties of different antioxidants, including vitamin E and C [53,54,95]; α-lipoic acid [20]; N-acetyl cysteine [1] and Coenzyme Q10 [77]. Carotenoids have been suggested as novel therapeutic molecules against neurodegenerative disorders, as they have shown promising preventive activity and a slowdown effect on the progression of neurodegenerative diseases [43]. In Alzheimer's disease, these effects have been associated with the capacity of different carotenoids, including astaxanthin, to inhibit Amyloid-β (Aβ) peptide aggregation, as Aβ production and deposition is widely believed to drive this disease pathogenesis [55,71]. Astaxanthin-mediated neuroprotection has been mostly studied in animal and in vitro experimental models, including acute injuries, chronic neurodegenerative disorders, and neurological diseases, associating its benefits to anti-oxidation, anti-inflammation, and anti-apoptotic mechanisms [17,18,89,90].

Regarding clinical trials, in the last two decades, an increasing number of studies have reported the neuroprotective potential of astaxanthin as a novel therapy for the prevention or co-treatment of diseases like Alzheimer's, dementia, and other cognitive disorders; however, only a few of them have shown concluding results. For example, Katagiri et al. [38] studied the effects of astaxanthin ingestion on the cognitive function of 96 elderly subjects in a randomized, double-blind, placebo-controlled study. In this research, somatometry, hematology, urine screens, cognitive and maze learning tests were performed before and after 12 weeks of astaxanthin administration (6 or 12 mg/day). The results suggested that astaxanthin improves cognitive function in healthy aged individuals, as the treated subjects made fewer errors in the maze tests and demonstrated faster reaction times in Cog-Health (a computer-based test of memory and thinking capability tests). However, the authors did not find statistical differences between the treated and placebo groups, indicating this was probably due to the small-sized samples. Hayashi et al. [27] also studied the effect of an astaxanthin-rich extract on the cognitive function in middle-aged and older individuals, reporting significant improvements ($p < 0.05$) in a word memory test in <55-year-old subjects supplemented with astaxanthin, when compared with a placebo group. However, no significant improvement was found in ≥55-year-old subjects. In another randomized, double-blind, placebo-controlled trial, comprising twenty-one healthy participants with mild cognitive impairment, a composite supplement consisting of astaxanthin (3 mg/) and sesamin (5 mg) was administered daily to the treated group. The results showed a significant improvement ($p < 0.05$) in psychomotor and processing speed when comparing the supplemented group to the placebo group after 12 weeks of dietary supplementation [34]. Even though the results are promising, the authors did not further investigate if the observed improvement of cognitive functions was derived from either astaxanthin, sesamin, or a synergistic effect of both antioxidants.

The effects on mental and physical fatigue have also been studied, reporting a reduction in the daily sense of fatigue caused by both mental and physical loads after supplementation with astaxanthin (12 mg/day) for 12 weeks in a randomized, placebo-controlled, parallel-group study conducted by Hongo et al. [29]. Imai et al. [31] reported similar results as soon as four weeks on his study, with a 5 mg sesamin/3 mg astaxanthin supplement ($p < 0.05$).

As mentioned previously, in vivo oxidation of fatty acids has been reduced in subjects supplemented with astaxanthin [37]. This can be especially relevant for patients who have Alzheimer's and dementia, as phospholipid hydroperoxides (PLOOH) accumulate abnormally in the erythrocytes of patients suffering from these diseases [52,62]. The randomized, double-blind, placebo-controlled human trial conducted by Nakagawa et al. [62] concluded that astaxanthin supplementation (6 and 12 mg/day) resulted in improved erythrocyte antioxidant status

($p < 0.01$), reducing PLOOH levels in middle-aged and senior subjects, suggesting that astaxanthin may contribute to the prevention of dementia.

3.5. Immune response

Even though the potential benefits of astaxanthin on the immune system have been poorly studied in humans, promising results have been reported. The first reported human trial was carried out in 2010, consisting of a randomized, double-blind, placebo-controlled study which assessed the immune response of healthy young female subjects after administration of astaxanthin (0, 2, or 8 mg/day) for eight weeks [69]. The results showed that dietary astaxanthin (8 mg) stimulated mitogen-induced lymphoproliferation, rose natural killer cell cytotoxic activity, and increased total T and B cell subpopulations, demonstrating an immune-enhancing effect. The mucosal immune system plays an important role as the first line of defense against pathogen invasion, preventing the attachment of infectious agents to mucosal surfaces [47]. In this context, another trial assessed the effect of astaxanthin supplementation on salivary IgA (sIgA) [7], an antibody that largely dominates mucosal humoral immunity [12]. In this study, forty male soccer players were randomly assigned to astaxanthin supplementation (4 mg/day) or placebo groups. After 90 days of supplementation, the results showed a significant increase ($F = 6.221$, $p < 0.05$) in sIgA levels, suggesting that astaxanthin could show significant physiologic modulation in individuals with mucosal immunity impairment. Andersen et al. [5] developed a study with 44 patients with gastric inflammation and functional dyspepsia produced by *H. pylori*. A significant ($p < 0.05$) up-regulation of CD4 T-lymphocytes ("helper" lymphocytes that activate macrophages or B lymphocytes, involved in immunity against bacteria and protozoa) and down-regulation ($p < 0.01$) of CD8 T-lymphocytes, known as cytotoxic cells activated by virally infected cells [25], was observed in patients treated with 40 mg/day of astaxanthin. However, no changes were found in the density of *H. pylori*. In this study, astaxanthin administration may have favored a more accurate immune response to *H. pylori* colonization. To our knowledge, the results reported by Park et al., Baralic et al., and Andersen et al., are at present the only existing data on human trials regarding the role of astaxanthin in the immune response.

4. Discussion

Growing evidence of astaxanthin benefits on human health has been reported, validating its consumption for the prevention or co-treatment of several diseases, especially those related to oxidative stress and aging. Its demonstrated benefits, together with an important part of the world population interested in leading healthier lifestyles, have made astaxanthin a highly demanded antioxidant, with a global market size that is expected to grow from $USD 600 million in 2018 to 880 million by 2024 [100]. Nowadays, natural astaxanthin products can be found in dosage forms as tablets, capsules, syrups, oils, soft gels, creams, biomass, and granulated powders [4], and no safety concerns have been reported regarding its consumption, as reviewed extensively by Brendler and Williamson (2019). Even though several of its benefits have been demonstrated in the clinical trials reviewed in this article, these have been shown to vary according to the astaxanthin source, its isomeric variant, and even the consumers' diet. This may be one of the reasons why contradictory results have been found when assessing same parameters and pharmacokinetics of astaxanthin in different studies. In humans, the bioavailability of carotenoids is low and variable, ranging from 10% to 50% of a given dose [58]. This is a result of their low solubility/dispersibility in gastrointestinal tract juices, compromising the uptake of astaxanthin by intestinal epithelial cells and their final secretion to lymph as chylomicrons [99]. It has been reported that astaxanthin bioavailability is enhanced when taken together with dietary lipids, suggesting that a high cholesterol diet may increase carotenoid absorption, while a low-fat diet reduces it [4,101]. Odeberg et al. [65] studied the pharmacokinetics of astaxanthin by administering a single dose of 40 mg astaxanthin to healthy male volunteers, either as a commercially available food supplement or as lipid based formulations. Lipid based formulations, containing long-chain triglyceride (palm oil) or glycerol mono- and dioleate, showed significantly ($p < 0.05$) enhanced bioavailability, ranging from 1.7 to 3.7 times than the reference formulation. This results show the need to develop better astaxanthin delivery systems, like nanoformulations and targeted therapy, to improve its bioavailability in different target groups [18]. To date, only few studies have assessed pharmacokinetic parameters of astaxanthin-based formulations in humans, however, interesting results have been reported in animal models. For example, Singh et al. [78] investigated the relationship between globule size and tissue distribution of different types of astaxanthin formulations, namely macro, nano and oil solution administered to rats, concluding that nano sized emulsions improve tissue distribution and enhance astaxanthin's bioavailability. Also, the highest concentrations of astaxanthin were found in the spleen (1673.28 ± 99.86 μg/g wet weight). These results may explain astaxanthin's pronounced effect on the immune system, as reviewed in this article. High concentrations in the spleen were followed by the kidney, suggesting this is the primary excretion organ of astaxanthin. The level of total concentration in descending order was showed to be spleen, kidney, heart, lung and liver.

Here, we reviewed several human clinical trials with promising results, but there are still numerous benefits demonstrated only in animal or in vitro models. For example, regarding eye health, effects of astaxanthin on uveitis (inflammation and irritation of the uvea, the middle layer of the eye, which supplies most of the blood flow to the retina) have been studied in rats with positive results. Endotoxin-induced uveitis was suppressed when administering astaxanthin to rats in a dose-dependent fashion, with an ocular anti-inflammatory effect of 100 mg/kg, as strong as that of 10 mg/kg of the anti-inflammatory control prednisolone [67,83]. *In vitro* assays carried in the same study using RAW264.7 cells (a macrophage model cell line) also demonstrated that astaxanthin decreased the production of inflammatory markers such as nitric oxide (NO), prostaglandin E2 (PGE2), and tumor necrosis factor (TNF-α). Antitumor activity of astaxanthin has also been widely studied in animal and in vitro models, showing anti-proliferative, anti-apoptosis, and anti-invasion activity. Recently, McCall et al. [48] demonstrated that astaxanthin blocks the proliferation and reduces cell number in breast cancer tumors. Also, when compared to other carotenoids like canthaxanthin and β-carotene, astaxanthin has shown the highest mammary tumor growth inhibition in mice (Chew et al., 1999). Numerous interesting results regarding the anticancer activity of astaxanthin can be found in the review by Zhang and Wang (2015). Nowadays, neurodegenerative diseases may be one of the most critical concerns for public health, as they are a growing cause of mortality and morbidity worldwide. As mentioned above, even though promising, contradictory results have been found in this context. Several theories of the possible reasons for little efficacy of antioxidants in treating neurodegenerative diseases, including an insufficient dose of antioxidants, inconvenient timing for therapy, or inappropriate duration of treatments. Regarding timing, as reviewed by Kim et al. [40], most clinical trials have assessed the efficacy of antioxidants in patients with advanced Alzheimer's or Parkinson's disease. However, antioxidants may play a preventive role, suggesting that an earlier supplementation, even before the onset of symptoms, may be more effective. It is also possible that the oxidative damage may not be the primary cause of the neurodegenerative disease in some patients, suggesting that antioxidants should be combined with other drugs for their treatment [40].

In conclusion, even though there is still a long way to go in order to ensure its effectiveness, the studies and findings so far revised and discussed in this review suggest astaxanthin may be a promising candidate for the prevention and co-treatment of several diseases associated with oxidative stress and aging.

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Conflict of interest

The authors declare that this research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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