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Review Article

Human Health Benefits of Astaxanthin Derived from *Haematococcus pluvialis*: A Review

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Abstract

The carotenoid astaxanthin has received attention for its strong antioxidant activity and related health benefits. It demonstrates higher activity than other antioxidants and carotenoids, such as β-carotene and lycopene which is most likely due to its unique polar structure and ability to donate electrons and stabilize free radicals. It is thought to stimulate endogenous antioxidant production. Numerous reports support multiple health benefits for natural astaxanthin. These include benefits related to cardiovascular health, diabetes, exercise, brain, skin and eye health. It is also known for its anti-inflammatory, anti-apoptotic, neuroprotective and cardioprotective effects. It is well tolerated, bioavailable and safe. It is the purpose of this comprehensive review to present human research from 2000 to the present on the human health benefits of naturally derived astaxanthin from *Haematococcus pluvialis*. Studies assessing synthetic astaxanthin or multi ingredient supplements were excluded.

Keywords: *Carotenoid; Astaxanthin; Haematococcus pluvialis; Inflammation; Antioxidant*

Abbreviation

FDA: The United States Food and Drug Administration; GRAS: Generally Recognized as Safe; ROS: Reactive Oxygen Sub-Species; Nrf-2: Nuclear Factor Erythroid2-Related Factor 2; HO-1: Heme Oxygenase-1; MDA: Malondialdehyde; ISP: Isoprostane; SOD: Superoxide Dismutase; TAC: Total Antioxidant Capacity; CVD: Cardiovascular Disease; TG: Triglycerides; NK: Natural Killer Cell; DTH: Delayed-Type Hypersensitivity; TNFα: Tumor Necrosis Factor Alpha; IL-2: Interleukin-2; IFN-γ: Interferon-Gamma; DOMS: Delayed Onset Muscle Soreness; CPT1: Carnitine Palmitoyl Transferase; sIgA: Secretory Immunoglobulin A; CK: Creatine Kinase; AeT: Aerobic Threshold; AT: Anaerobic Threshold; AD: Alzheimer's Disease; PD: Parkinson's Disease; HD: Huntington's Disease; ALS: Amyotrophic Lateral Sclerosis; PLOOH: Phospholipid Hydroperoxides; RSSC: Residual Skin Surface Components; AMD: Age-Related Macular Degeneration; DM: Diabetes Mellitus

Introduction

Carotenoids have been the focus of considerable scientific research and popular attention in recent decades, due to their well-documented health benefits, including antioxidant functions such as cell repair, anti-aging and anti-inflammatory effects, as well as reversal of skin damage from UV rays [1,2]. Carotenoids are classified by their chemical composition as either carotenes (e.g. β-carotene, lycopene, etc.) or xanthophylls (e.g. canthaxanthin, astaxanthin, etc.). Carotene carotenoids demonstrate adequate antioxidative properties at lower concentrations but, conversely, demonstrate prooxidative activity at higher concentrations. In contrast, xanthophyll carotenoids such as astaxanthin demonstrate only antioxidant activity throughout the concentration range without demonstrating any prooxidative properties [3].

The physiological effects of carotenoids vary according to their polarity, which dictates the way in which they configure with cellular membranes. "Lycopene and β-carotene are non-polar and disorder the membrane bilayer and stimulate membrane lipid peroxidation (> 85% increase in lipid hydroperoxide levels), whereas astaxanthin (a polar carotenoid) preserves membrane structure and exhibits significant antioxidant activity (> 40% decrease in lipid hydroperoxide levels)". These results suggest that the antioxidant potential of carotenoids is dependent on their distinct membrane lipid interactions [4]. In fact, its unique conjugated polyene central chain and hydroxy and keto moieties on each ionone ring help it to scavenge singlet oxygen and free radicals. This unique structure allows it to span the entire cross-sectional width of cell membranes, such that its polar ends orient themselves towards the polar regions of cell membranes which enhances its membrane function. Both the polarity and unique length of astaxanthin help to explain why its membrane-strengthening aspect provides antioxidant effects that are superior to other carotenoids [5-7]. In addition, it has more potent singlet oxygen quenching ability than other antioxidants [7].

Astaxanthin has three stereoisomers: 3R,3'R, 3R,3'S and 3S,3'S. Yeast *Xanthophyllomyces dendrorhous* produces (3R, 3'R)-isomer, synthetic astaxanthin comprises isomers of (3S, 3'S) (3R, 3'S) and (3R, 3'R). This is the primary stereoisomer of astaxanthin found in the Antarctic krill *Euphausia superba* is 3R, 3'R which contains mainly esterified form and in wild Atlantic salmon it is 3S, 3'S which occurs as the free form. Astaxanthin produced by natural sources such as the microalgae *Haematococcus pluvialis* (*H. pluvialis*) consists of the 3-S,3'-S stereoisomer. Microalgae produce astaxanthin as a survival mechanism when exposed to stressful conditions, because it protects the algae against extreme temperatures and allows the algae to survive for many years without food or water [5]. It can be grown in open ponds, outdoor tube systems and indoor systems under artificial light and is found in most red-colored aquatic organisms such as lobster and salmon, which utilize algae as a food source. The green microalga *H. pluvialis* has the greatest capacity to synthesize astaxanthin, up to 4 - 5% of dry weight [8]. *H. pluvialis*, it is the type most commonly ingested by humans [6,9,10]. The activity of astaxanthin is most likely due to its chemical structure, specifically in stereochemistry and esterification, as well as the fact the natural astaxanthin contains small amounts of other carotenoids and beneficial fatty acids and synthetic versions do not. The United States Food and Drug Administration (FDA) has approved the use of astaxanthin as food colorant in animal and fish feed and plant-derived astaxanthin is generally recognized as safe (GRAS) by the FDA. The European Commission considers natural astaxanthin as a food dye [11].

Astaxanthin is well tolerated and no toxic effects have been reported [12]. Astaxanthin from *H. pluvialis* is more bioavailable than other carotenoids, probably because of the presence of astaxanthin esters [13,14]. Maximal blood astaxanthin concentration occurred between 8 and 10h after intake of 40 mg in healthy adults (n = 32) [15,16]. Similar times of 6.7 ± 1.2h (n = 3) and 11.5 h (n = 3) were also observed after doses of 100 mg [17,18]. Following the consumption of 40 mg, a half-life of 15.9 ± 5.3 h has been reported [15]; half-lives of 21 ± 11 and 52 ± 40 h have been following consumption of a 100 mg dose [17,18].

Numerous epidemiologic studies have reported that diets high in fruits and vegetables correlate with a reduced risk for certain cancers, cardiovascular disease, age-related macular degeneration, Alzheimer's disease and arthritis [19-23]. Oxidative stress and the associated free radical damage to many cells and structures such as DNA, proteins and lipids, are believed to be major factors in the pathogenesis of such diseases. One of the benefits of an increased intake of fruits and vegetables is the associated increased intake of antioxidants, including carotenoids [3,24,25]. This results in a decrease in oxidative stress and associated inflammation, which have been identified as key factors in many diseases. Therefore, due to its' potency as an antioxidant, it is reasonable to explore the effects of astaxanthin on maintaining health, relative to its antioxidant and anti-inflammatory effects. It is the purpose of this comprehensive review of publications from 2000 to the present to examine research on the human health benefits of natural algae-derived astaxanthin (Table 1). Using the search engines Pub Med and Google Scholar, animal studies, studies using synthetic astaxanthin or multi-ingredient supplements and studies that were not well-controlled were excluded.

Author	Dose of Astaxanthin	Subjects	Duration	Effects
Kim., *et al*. 2011 [26]	5,20,40 mg/day	Smokers compared to non-smokers	3 wk	↓ MDA (Dose dependent) ↓ ISP ↑ SOD ↑ TAC
Yoshida., *et al*. 2010 [27]	0,6,12,18 mg/day	61 non-obese aged 25-60 yrs TG 120-200 mg/dl	12 wk	↓TG (12, 18 mg)* ↑HDL (6, 12 mg)* ↑ adiponectin*
Iwamoto., *et al*. 2000 [28]	1.8, 3.6, 14.4, 21.6 mg/day	24 healthy	14 d	↑ time to LDL oxidation* (3.6 -21.6 mg/day)
Karppi., *et al*. 2007 [29]	8 mg	Men 19-33	12 wk	↑ plasma astaxanthin levels* ↓ in vivo oxidation of fatty acids* well tolerated
Choi., *et al*. 2011 [30]	5, 20 mg/day	27 Obese and overweight	12 wk	↓ MDA* ↓ isoprostane* ↑ SOD* ↑ Total antioxidant capacity* ↓ LDL* ↓ ApoB*
Ursoniu 2016 Meta-analysis of 7 RCTs [31]	4-20 mg/day	280 subjects	4-12 wk	↓ fasting blood sugar* No change in lipid profiles
Earnest., *et al*. 2011 [32]	4 mg/day	14 competitive cyclists	28 d	↑ power* ↓ time* No change in CHO or fat metabolism
Res., *et al*. 2013 [33]	20 mg/day	32 trained male cyclists	4 wk	↑ plasma astaxanthin * No increase in antioxidant capacity No change in MDA No change in fat oxidation No ↑ performance
Baralic., *et al*. 2015 [34]	4 mg/day	40 Male Soccer Players	90 days	↑sIgA ↓ prox/antiox balance Blunt CRP Blunt neutrophil Decrease muscle damage Decrease inflammation
Klinkenberg 2013 [35]	20 mg/day	32 well trained male cyclists	4 wk	↑ plasma astaxanthin * No change in cardiac troponin t concentrations No change in antioxidant capacity No change in c reactive protein or creatine kinase

Talbott., *et al*. 2017 [36]	12 mg/day	28 recreational runners	8 wk	↓ lower sub max HR ↓ aerobic threshold ↓ anaerobic threshold No change VO2 max No change max power output
Fry., *et al*. 2004 [37]	8 g/day	9 Weight trained men	3 wk	↓ DOMS
Katagiri., *et al*. 2012 [38]	6, 12 mg/day	96 middle aged and elderly complaining of forgetfulness	12 wk	↑ Cog health battery scores (12 mg) ↑ Groton Maze Learning test scores (6,12 mg)
Nakagawa., *et al*. 2011 [39]	6, 12 mg/ day	30 middle aged and elderly	12 wk	↑ Astaxanthin in erythrocytes (6, 12 mg/d) ↓ PLOOH (which increase in dementia) (6,12 mg/d)
Tominaga., *et al*. 2012 [40]	6 mg/day 2 ml topical	30 women 36 males	8 wk 6 wk	↓ skin wrinkle ↓ age spot size ↑ elasticity ↑moisture ↑ texture ↑ corneocyte condition
Chalyk., *et al*. 2017 [41]	4 mg/day	17 men and 14 women	4 wk	↓Malondialdehyde ↓RSCC
Akira., *et al*. 2004 [42]	4, 12 mg/day	49 subjects over 40 yrs	28 d	↑ far site acuity ↓ accommodation time
Sawaki., *et al*. 2002 [43]	6 mg/day	20-year-old men	4 wk	↑ Deep vision ↑ Critical flicker fusion
Nagaki., *et al*. 2006 [44]	6 mg/day	40 healthy subjects	4 wk	↓ Eye fatigue
Yasunori., *et al*. 2005 [45]	6 mg/day	18 subjects	4 wk	↑ retinal capillary blood flow
Mashadi., *et al*. 2018 [46]	8mg/day	44 subjects	8 wk	↑ Adiponectin* ↓ visceral fat ↓TG; VLDL ↓ Systolic BP
Chen., *et al*. 2019 [47]	6 mg/day 12 mg/day	54 subjects	8 wk	↓ FBG and HbA1c* ↓ IL-6; TNF-Alpha 12 mg: ↓ TG, TC, LDL ↓ FVII; PAI-1

Table 1: *Summary of Human Studies from 2000 to the present supplementing algae-derived Astaxanthin on various health benefits.*

**Indicates significant results p<.05.*

Antioxidant capacity

Astaxanthin is a strong antioxidant, demonstrating greater protection against lipid peroxidation than vitamin E both *in vivo* and *in vitro* [48] and singlet oxygen quencher capacity 11 times more powerful than β -carotene [49]. This may be directly related to its structure [50] and may account for its increased potency compared to other carotenoids such as β -carotene [49,51], vitamin C, zeaxanthin, lutein

and canthaxanthin [52]. Within the cell membrane, lipophilic astaxanthin functions as an antioxidant by directly scavenging cellular free radicals such as reactive oxygen sub-species (ROS) through the mechanism of donating electrons and terminating free radical peroxidation chain reactions [24,25]. At the cell surface, it maintains mitochondria in the reduced redox state, thus promoting functional integrity and it activates antioxidant signaling [53-56]. It has been reported that astaxanthin, at amounts consumed through diet or supplementation, does effectively improve mitochondrial function because it maintains the mitochondria in the reduced state [50]. It donates electrons and stabilizes free radicals terminating the damaging free radical chain reaction [24,25].

Although several hypotheses exist, the precise cellular mechanism by which astaxanthin exerts its antioxidant effect is not known, nor is the precise dosage required for optimal intracellular activity. A study to determine antioxidant response in human umbilical vein endothelial cells reported that the antioxidant function of astaxanthin may not be to directly scavenge free radicals, which is the prevailing theory, but may actually activate the cellular antioxidant defense system by activating the nuclear factor erythroid2-related factor 2 (Nrf-2)/heme oxygenase-1 (HO-1) signaling pathway. This promotes the generation of small amounts of ROS in cells, thus stimulating an endogenous defense. The authors speculated that astaxanthin-induced generation of trace amounts of ROS may act as a secondary signal to activate a specific antioxidant pathway [57].

It has been suggested that astaxanthin may provide important oxidative protection for individuals experiencing excessive oxidative stress, e.g. obese individuals and smokers [30]. Thirty-nine heavy smokers and 39 non-smokers (controls) were randomly assigned to receive either 5, 20 or 40 mg/day of astaxanthin for 3 weeks and oxidative stress markers were assessed. Compared to baseline, in smokers the oxidative markers malondialdehyde (MDA) and isoprostane (ISP) decreased at all doses, in a dose-dependent manner and antioxidant capacity, as measured by superoxide dismutase (SOD) and total antioxidant capacity (TAC), increased, suggesting that astaxanthin may help offset some of the oxidative damage associated with smoking [26].

Numerous studies have suggested multiple health benefits associated with consumption of natural astaxanthin based on its chemistry, mechanism of action and antioxidant properties in both *in vitro* and *in vivo* models [24,27,50]. As a result of its role as an antioxidant, astaxanthin also known for its anti-inflammatory, antiapoptotic, neuroprotective and cardioprotective effects [24,53]. Kim., *et al.* [26] for a review of its effects on oxidative stress-induced mitochondrial dysfunction [58].

Cardiovascular effects

In addition to the antioxidant associated benefits of astaxanthin, several studies have reported that astaxanthin is involved in the prevention of atherosclerosis via its potential to reduce inflammation and improve lipid and glucose metabolism [6,27-30]. In several studies using rabbit [59] and rodent models [60,61], it has demonstrated a beneficial cardiovascular effect. In some clinical trials, other carotenoids, such as β-carotene, had no beneficial effects on endpoints associated with cardiovascular disease (CVD) [26,62] and acted as pro-oxidants at higher doses [6]. As mentioned previously, one of the potential mechanisms associated with astaxanthin that makes it an effective antioxidant is that it does not act as a pro-oxidant [4]. In a 12-week, placebo-controlled, dose- response randomized trial, the consumption of natural algae-derived astaxanthin doses of 6, 12, 18 mg/day resulted in a significant decrease in serum triglycerides (TG) levels, an increase in serum HDL-cholesterol levels and an increase in serum adiponectin levels in adult subjects with mild hyperlipidemia [27]. TG levels were reduced for the 12 and 18 mg/day groups and HDL and adiponectin levels were increased for the 6 and 12 mg/day groups. Increases in adiponectin have been reported to correlate inversely with TG levels, by means of increased VLDL catabolism. Its direct correlation with HDL-cholesterol changes, independent of age and BMI, is thought to be via liver X receptor gamma and PPAR alpha systems that enhances HDL-associated Apo-A1 release [27]. While the relationship between astaxanthin and adiponectin is not completely understood, the authors suggest that the anti-inflammatory effects of astaxanthin may be due to its corresponding ability to increase adiponectin levels, because adiponectin itself has anti-inflammatory effects [27].

In a similar study, 24 subjects consumed astaxanthin at doses of 1.8, 3.6, 14.4 and 21.6 mg per day for 14 days. Following astaxanthin consumption, LDL-cholesterol lag time to oxidation was longer (5.0, 26.2, 42.3 and 30.7% respectively) compared with day 0, but there was no difference in oxidation of LDL between day 0 (lag time 59.9+/-7.2 min) and day 14 (57.2+/-6.0 min) in the control group. The authors concluded that astaxanthin inhibits LDL oxidation, which may contribute to the prevention of atherosclerosis, as oxidized LDL-cholesterol is an independent risk factor for CVD [28]. In a randomized, double-blind study of healthy men, aged 19 - 33 years, the effects of a three-month supplementation period with 8 mg/day of astaxanthin (in capsule form) on astaxanthin absorption and lipid peroxidation were assessed. Supplementation with astaxanthin resulted in an increase in plasma astaxanthin levels compared with the placebo group ($p < 0.001$). Levels of *in vivo* oxidation of fatty acids, as measured by plasma 12- and 15-hydroxy fatty acids, were reduced significantly in the astaxanthin group ($p = 0.048$ and 0.047 respectively), but not in the placebo group and the change of 15-hydroxy fatty acid was greater with a trend towards significance ($p = 0.056$) in the astaxanthin group, compared to the placebo group. This study suggested that intestinal absorption of encapsulated astaxanthin was successful and well tolerated and that supplementation with astaxanthin decreased *in vivo* oxidation of selected fatty acids in healthy men [27]. In another study, obese and overweight adults consuming 5 and 20 mg/day of astaxanthin for 3 weeks decreased blood levels of MDA and ISP and increased blood levels of SOD and TAC. In addition, subjects consuming astaxanthin had lowered LDL-cholesterol and Apolipoprotein B (ApoB) levels [30]. However, additional studies are needed to identify appropriate dosages and to assess overall efficacy as a possible preventative measure against CVD.

Immune system effects

Astaxanthin's proposed function as an antioxidant helps to explain its role in reducing inflammation and improving immunity. In a double blind, placebo-controlled study, 14 female college-age students consumed a placebo, 2 mg/day or 8 mg/day of astaxanthin for 8 weeks. Astaxanthin absorption and immune response were assessed at 4 and 8 weeks and plasma astaxanthin levels increased ($P < 0.01$) dose-dependently. DNA damage, as assessed by measuring plasma 8-hydroxy-2'-deoxyguanosine (8-OHdG), was decreased in both the 2 and 8 mg/day groups at both 4 and 8 weeks, with no significant difference between week 4 and week 8 levels. Lipid peroxidation, measured by plasma concentrations of 8-epi-prostaglandin F2a, was unaltered by astaxanthin supplementation. Plasma C-reactive protein concentration was lower ($P < 0.05$), but only in subjects taking 2 mg astaxanthin for 8 weeks. Dietary astaxanthin stimulated mitogen-induced lymphoproliferation, increased natural killer (NK) cell cytotoxic activity and increased total T- and B-cell subpopulations, but did not influence populations of T-helper, T-cytotoxic or NK cells. Subjects consuming 2 mg/day of astaxanthin for 8 weeks had a higher percentage of leukocytes expressing the LFA-1 marker and a higher tuberculin response, a measure of delayed-type hypersensitivity (DTH), than those in the placebo group. There was no difference in tumor necrosis factor alpha (TNFα) and Interleukin-2 (IL-2) concentrations, but plasma Interferon-gamma (IFN-γ) and IL-6 levels increased by week 8 in subjects taking 8 mg/day of astaxanthin. The authors concluded that supplementation with astaxanthin enhanced immune response and decreased DNA damage in healthy female subjects [63]. Additional studies with larger groups of subjects representing both genders and a variety of age groups would contribute to the literature regarding the role of astaxanthin in immunity.

Exercise and exercise recovery effects

While there is a paucity of information regarding the mechanism by which astaxanthin supports immune function, there is evidence to support its role in inflammation related to exercise training. Production of ROS is an unavoidable outcome of exercise and it can be significantly increased as a result of intense training. During aerobic activity, ROS production increases in the mitochondria and this can sometimes overwhelm the body's abilities to produce natural antioxidants [54,55,64]. An increase in ROS has been suggested as a cause of delayed onset muscle soreness (DOMS). Astaxanthin may decrease symptoms related to DOMS by reducing production of ROS and related inflammation.

Previous animal studies have suggested that this carotenoid enhances exercise metabolism, performance and recovery [65,66]. Because astaxanthin is lipophilic, it accumulates in the mitochondrial membrane and therefore provides a protection against the accumulation of ROS [54,55]. It has been suggested that astaxanthin enhances fat metabolism during exercise by decreasing ROS, thereby protecting the mitochondrial carnitine palmitoyl transferase (CPT1), which is required to transfer long chain fatty acids into the mitochondria for energy utilization. CPT1 is a key regulatory step in fat metabolism which can be modulated by the accumulation of ROS [67]. While an interesting potential mechanism of action, it has yet to be replicated in human research [32,33]. For example, Res., *et al*. reported that 4 weeks of supplementation with 20 mg/day of natural astaxanthin, in 32 trained male cyclists, did not lead to significantly greater TAC or attenuated MDA, even though plasma levels of astaxanthin were significantly increased in the group taking the supplement. Furthermore, whole body fat oxidation did not change over time within each group, or between the treatment and placebo groups. In addition, there was no improvement in time trial performance. The authors suggest that the lack of beneficial results may be due to the short supplementation time, i.e. 4 weeks compared to 12 weeks in other studies and to the high fitness level of the subjects in their study as high fitness levels are associated with increased endogenous antioxidant levels [33].

Similarly, Earnest., *et al*. examined cycling time trial performance in 14 competitive cyclists following 28 days of supplementation with either 4 mg/day of natural algae-derived astaxanthin or a placebo. They reported a significant improvement in time (5% decrease in a 20 km cycle trial) and 15% increase in power in time trial performance, but no change in fat or carbohydrate metabolism, leaving the improvements in performance unexplained. Again, the high fitness levels of these subjects may explain the results [32]. In a 4-week study of 32 well-trained cyclists consuming 20 mg/day of natural astaxanthin for 4 weeks, neither exercise-induced cardiac troponin T concentrations nor antioxidant capacity were improved, despite a significant increase in plasma astaxanthin concentrations [35]. This further supports the hypothesis that subject fitness level may attenuate the beneficial effects of astaxanthin on lipid peroxidation during exercise.

Another, aspect to consider is the intensity of the exercise; when studying lipid metabolism perhaps lower intensity exercise should be utilized during a time trial as lower intensity exercise is more likely to use fat as an energy source. In a double-blind placebo-controlled study of 40 male soccer players participating in intense training and consuming 4 mg/day of astaxanthin for 90 days, there was a significant increase of both secretory immunoglobulin A (sIgA) absolute concentration and its secretion rate, when compared to baseline values ($p < 0.05$), while there were no significant changes in the placebo group. A significant decrease in creatine kinase (CK) activity, a marker of muscle damage, compared to baseline values ($p < 0.01$), was reported, while a decrease in the placebo group was not statistically significant. In addition, there was a decrease in pro-oxidantantioxidant balance (PAB) and the increase in neutrophil count and hs-CRP level recorded in the placebo group was not apparent in the supplemented group. This is indicative of a significant blunting of the systemic inflammatory response in the subjects consuming astaxanthin. This study suggests that astaxanthin may attenuate muscle damage, improve sIgA response and blunt the inflammatory response to intense exercise training [34]. Similarly, in a double-blind parallel study, 28 recreational runners (male = 14, female = 14, age = 42) were supplemented with 12 mg/day astaxanthin for 8 weeks. While subjects consuming the supplement experienced no improvement in VO2 max or maximal power output, they exhibited a significant approximately 10% lower average heart rate at submaximal running intensities compared to placebo (aerobic threshold (AeT); natural astaxanthin 130 + 17 vs. placebo 145 + 14; and anaerobic threshold (AT); astaxanthin 139 + 20 vs. placebo 154 + 11, $p < 0.05$ for combined AeT and AT results). These results suggest that supplementation may benefit endurance athletes as compared to high intensity athletes [36]. In a study in weight-trained individuals with a high percentage area for fiber types IIA and IIAB/B consuming 8 g/day of astaxanthin for 3 weeks, it was reported that astaxanthin supplementation "may preferentially attenuate perceptions of DOMS in weight trained men with a high % area for fiber types IIA and AB/B" [37]. Brown., *et al*. [12] offer a more comprehensive review of this specific topic than is appropriate for this document [12].

Brain health effects

Astaxanthin has been reported to exert a strong protective effect on the human brain, due at least in part to its chemical structure, which allows it to cross the blood-brain barrier [68]. Considering that oxidative damage and neural inflammation have been implicated in the pathogenesis of several neurodegenerative conditions such as Alzheimer's Disease (AD), Parkinson's Disease (PD), Huntington's disease (HD) and amyotrophic lateral sclerosis (ALS), there is increasing interest in the use of natural antioxidants and anti-inflammatory agents in the attenuation or possibly even the prevention of such conditions. While these diseases have different factors that contribute to their development and progression, oxidative stress is an aspect of their etiology [69]. Galasso., *et al*. offer a complete review of the neuroprotective role of astaxanthin [69].

Several studies have shown that astaxanthin helps to offset the progression of cognitive disorders in both *in vivo* and *in vitro* models for neurodegenerative diseases [47,68,38,70]. *In vitro* studies have suggested that astaxanthin's protective effects on neurodegenerative diseases may be due to its antioxidant-associated mitochondria protection; thus, it may prove to be effective in attenuating the oxidative stress-associated neurodegeneration associated with PD and other similar conditions [71-73]. In a randomized, double-blind, placebo-controlled study, 96 healthy middle-aged and elderly subjects who complained of age-related forgetfulness consumed either 6 or 12 mg of *H. pluvialis* extract or a placebo capsule for a period of 12 weeks. CogHealth is a computer-based method for the measurement of decision-making, attention and memory. CogHealth scores improved in the high-dosage group after 12 weeks. Groton Maze Learning Test scores improved in both the low-dosage and high-dosage groups, compared to placebo group. While none of the results showed a significant improvement, probably due to small sample size, they do suggest a potential benefit in cognitive function [38].

Phospholipid hydroperoxides (PLOOH) have been shown to accumulate in the erythrocytes of dementia patients and dietary astaxanthin is thought to prevent the accumulation of the PLOOH. In a randomized, double-blind, placebo-controlled human trial to assess the efficacy of 12 weeks of astaxanthin supplementation (6 or 12 mg/d) on astaxanthin accumulation and PLOOH levels in the erythrocytes of thirty middle-aged and senior subjects, erythrocyte astaxanthin concentrations were higher in both the 6 and 12 mg astaxanthin groups, compared to the placebo group. Erythrocyte PLOOH concentrations were lower in the astaxanthin groups than in the placebo group and the authors suggest that these changes may contribute to the prevention of dementia [39]. Additional studies are needed to clarify dosages and efficacy.

Skin effects

Research has suggested that much of the sun damage that leads to aging effects, such as wrinkles, sagging skin and loss of collagen, is a result of an increased production of ROS that overwhelm the ability of endogenous antioxidant production and its ability to offset the damaging effects of ROS. Thus, it seems reasonable to assume that oral and/or topical antioxidant supplementation may be beneficial for the skin [74]. In a small open-label study of 30 women receiving 6 mg/day of oral *H. pluvialis*-derived astaxanthin and 2 ml (78.9 μM solution)/per day of topical application, Tominaga., *et al*. reported various improvements in wrinkles, size of age spots, elasticity, skin texture, corneocyte moisture content and general condition of corneocytes after either 4 or 8 weeks of supplementation The authors suggest that astaxanthin derived from *H. pluvialis* can improve skin condition in all layers of the skin as a result of combining oral supplementation and topical treatment [40].

They reported similar improvements in a randomized, double-blind, placebo-controlled study of 36 healthy males receiving the same supplement for 6 weeks [40]. Furthermore, age spots were lightened via astaxanthin's ability to suppress the oxidative polymerization in melanocytes and the inflammation in the epidermis [40]. The authors suggest that the benefits may be due to promotion of collagen fiber recovery as a result of astaxanthin protection of the dermal layer from singlet oxygen damage, which they reported in a previous *in vitro* study using human dermal fibroblasts [75]. Similarly, to assess the anti-aging potential of astaxanthin, 17 men and 14 women over the age of 40 consumed 4 mg/day of astaxanthin for 4 weeks. Plasma MDA levels decreased by 11.2% on day 15 and by 21.7% on day 29.

The analysis of residual skin surface components (RSSC) showed significantly decreased levels of corneocyte desquamation (P = 0.0075) and microbial presence (P = 0.0367). All of these changes are associated with characteristics of younger skin [41]. In a study of cultured human dermal fibroblasts, Suganuma., *et al*. reported that administration of astaxanthin immediately after UVA exposure significantly reduced the ROS cascade thought to be responsible for aging related to sun exposure [76]. For a comprehensive review of astaxanthin in skin health, repair and disease please see Davinelli, *etal*. 2018 [77].

Eye effects

Age-related macular degeneration (AMD) and age-related cataracts are among the leading causes of visual impairment and blindness. Both diseases appear to be related to oxidative and inflammatory processes [14,78]. Studies have shown that diets high in carotenoids, especially lutein and zeaxanthin, have been associated with a decreased risk for cataracts and AMD [79]. This is related to the fact that lutein and zeaxanthin are concentrated in the macula of the eye [80]. Astaxanthin is similar structurally to these carotenoids, however, it has demonstrated stronger antioxidant activity in restoring cells after UVA light-induced changes in antioxidant enzyme activity and lipid peroxidation [81]. Whether that effect translates directly to ocular cells is not clear. Studies in animals have demonstrated that astaxanthin is capable of crossing the blood–brain barrier and depositing in the retina of mammals in a manner similar to that of lutein. The majority of studies that have examined the protective role of astaxanthin on vision and eye fatigue have been performed on rats, however, they do suggest effectiveness in humans [14,78]. A study of 49 subjects over 40 years of age consuming either 4 or 12 mg of astaxanthin for 28 days reported significantly improved far visual acuity and shortened accommodation time [42]. Similarly, Sawaki., *et al*. reported significantly improved deep vision and critical flicker fusion in healthy adult male volunteers consuming astaxanthin [43]. Nagaki., *et al.* reported that 6 mg/day of astaxanthin improved visual display fatigue in terminal workers [44]. Yasunori has suggested that a possible mechanism of action of astaxanthin may be an increase retinal capillary blood flow in the eyes of healthy subjects [45]. Additional well-controlled studies in humans are required, but the potential for the benefits of astaxanthin in maintaining eye health is promising.

Diabetes mellitus effects

Human epidemiological research suggests an inverse correlation between plasma carotenoid concentration and the incidence of diabetes mellitus (DM) [82,83]. While most of the experimental research has involved rodent models [84], the role of astaxanthin as an antioxidant and anti-inflammatory agent supports the data from animal studies, suggesting that astaxanthin may assist in the prevention and/or symptom management of DM in humans [84]. Oxidative stress promotes insulin resistance in obesity and Type 2 diabetes; thus, an effective antioxidant may offer potential benefits [6]. A recent meta-analysis of data from 10 randomized controlled trials showed that astaxanthin supplementation lowered fasting blood glucose levels slightly [31]. In a double blind randomized controlled trial 54 type two diabetic patients took either 6 mg astaxanthin, 12 mg or placebo per day for 8 weeks. Astaxanthin supplementation lead to a significant decrease in fasting blood glucose levels and HbA1c and lowered plasma IL-6 and TNF-alpha levels. The higher dose lowered plasma triglycerides, total cholesterol and LDL levels and lowered clotting factors including plasminogen activator inhibitor and factor VII [85]. In a randomized controlled trial 44 subjects with type two diabetes took 8mg of Astaxanthin for 8 weeks or placebo. There was a significant difference in adiponectin, reduced visceral fat, a decrease in serum triglycerides, very low density lipoprotein (VLDL) and systolic blood pressure in the group taking astaxanthin compared to the placebo [46]. Several other studies have reported that carotenoids reduce type 2 diabetes risk in men and women [86-88], are inversely related to HbA1c levels [89] and have a protective role against diabetic retinopathy [90]. While more studies in humans are needed, it is important to consider that several mechanisms of action support the concept that astaxanthin and other antioxidants may influence aspects of diabetes. For example, the immune system causes inflammation via the release of chemokines and cytokines and carotenoids such as astaxanthin modulate the immune system activity through decrease of chemokines and cytokines via their antioxidant mechanisms. This directly impacts several of the complications associated with obesity, including diabetes [84].

Conclusion

In conclusion, human studies are supported by a plethora of animal *in vitro* and *in vivo* studies providing evidence that naturally derived astaxanthin is a unique antioxidant, due primarily to its structure and that it is superior to other antioxidants in both potency and function. Consumption of natural astaxanthin leads to multiple health benefits in humans. Table One provides a summary of studies from the year 2000 to the present time. Potential health benefits are related to cardiovascular health, diabetes, exercise, brain, skin and eye health and they are directly related to the antioxidant capacity and related anti-inflammatory effects of astaxanthin. Additional randomized controlled studies are required, particularly in healthy sub-clinical subjects seeking health benefits and disease prevention. In addition, future studies of dose-response characteristics will help to clarify adequate dosing levels for various desired benefits.

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Conflict of Interest

The author declares no conflict of interest.

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