Haematococcus astaxanthin: applications for human health and nutrition

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The carotenoid pigment astaxanthin has important applications in the nutraceutical, cosmetics, food and feed industries. *Haematococcus pluvialis* is the richest source of natural astaxanthin and is now cultivated at industrial scale. Astaxanthin is a strong coloring agent and a potent antioxidant – its strong antioxidant activity points to its potential to target several health conditions. This article covers the antioxidant, UV-light protection, anti-inflammatory and other properties of astaxanthin and its possible role in many human health problems. The research reviewed supports the assumption that protecting body tissues from oxidative damage with daily ingestion of natural astaxanthin might be a practical and beneficial strategy in health management.

Astaxanthin is the main carotenoid pigment found in aquatic animals and is present in many of our favorite seafoods including salmon, trout, red seabream, shrimp, lobster and fish eggs. It is also present in birds such as flamingoes and quails. In many of the aquatic animals in which it is found, astaxanthin has several essential biological functions including protection against oxidation of essential polyunsaturated fatty acids; protection against UV light effects; immune response; pigmentation; communication; reproductive behavior and improved reproduction [1]. Some microorganisms are rich in astaxanthin – the Chlorophyte alga *Haematococcus pluvialis* is believed to accumulate the highest levels of astaxanthin in nature. Commercially grown *H. pluvialis* can accumulate >30 g of astaxanthin kg^{-1} dry biomass [2].

Astaxanthin is closely related to other well-known carotenoids, such as β-carotene, zeaxanthin and lutein, thus they share many of the metabolic and physiological functions attributed to carotenoids. The presence of the hydroxyl and keto endings (Fig. 1) on each ionone ring, explains some unique features, such as the ability to be esterified, a higher anti-oxidant activity and a more polar configuration than other carotenoids. Free astaxanthin is particularly sensitive to oxidation. In nature, it is found either conjugated to proteins, such as in salmon muscle or lobster exoskeleton, or esterified with one or two fatty acids, which stabilize the molecule. In *H. pluvialis*, the esterified form predominates, mostly as astaxanthin monoester [1]. Various astaxanthin stereoisomers are found in nature that differ in the configuration of the two hydroxyl groups on the molecule (Fig. 1). The 3*S*,3′*S* stereoisomer is the main form found in *H. pluvialis* and in wild salmon [3].

Astaxanthin cannot be synthesized by animals and must be acquired from the diet. Although mammals and most fish are unable to convert other dietary carotenoids into astaxanthin, crustaceans (such as shrimp and some fish species including koi carp) have a limited capacity to convert closely related dietary carotenoids into astaxanthin, although they benefit from being fed astaxanthin directly. Mammals lack the ability to synthesize astaxanthin or to convert dietary astaxanthin into vitamin A: unlike β-carotene, astaxanthin has no pro-vitamin A activity in these animals [4].

Bioavailability and pharmacokinetics

The various steps of digestion, absorption and plasma transport of dietary carotenoids in mammals have been reviewed [5]. In the plasma, non-polar carotenoids such as β-carotene, α-carotene or lycopene, are mostly transported by very low density lipoproteins (VLDLs) and low density lipoproteins (LDLs) and polar carotenoids, such as zeaxanthin or lutein, are more likely to be transported by LDLs and high density lipoproteins (HDLs). The only study on humans to date confirmed the bioavailability of astaxanthin supplied in a single high dosage of 100 mg and its transport in the plasma by lipoproteins [6].

Astaxanthin as an antioxidant

Free radicals (e.g. hydroxyl and peroxyl radicals) and highly reactive forms of oxygen (e.g. singlet oxygen) are produced in the body during normal metabolic reactions and processes. Physiological stress, air pollution, tobacco smoke, exposure to chemicals or exposure to ultraviolet (UV) light, can enhance the production of such agents. Phagocytes can also generate an excess of free radicals to aid in their defensive degradation of the invader. Free radicals can damage DNA, proteins and lipid membranes. Oxidative damage has been linked to aging, atherogenesis, ischemia-reperfusion injury, infant retinopathy, age-related macular degeneration and carcinogenesis [7].

Dietary antioxidants, such as carotenoids, might help to prevent and fight several human diseases. Carotenoids are

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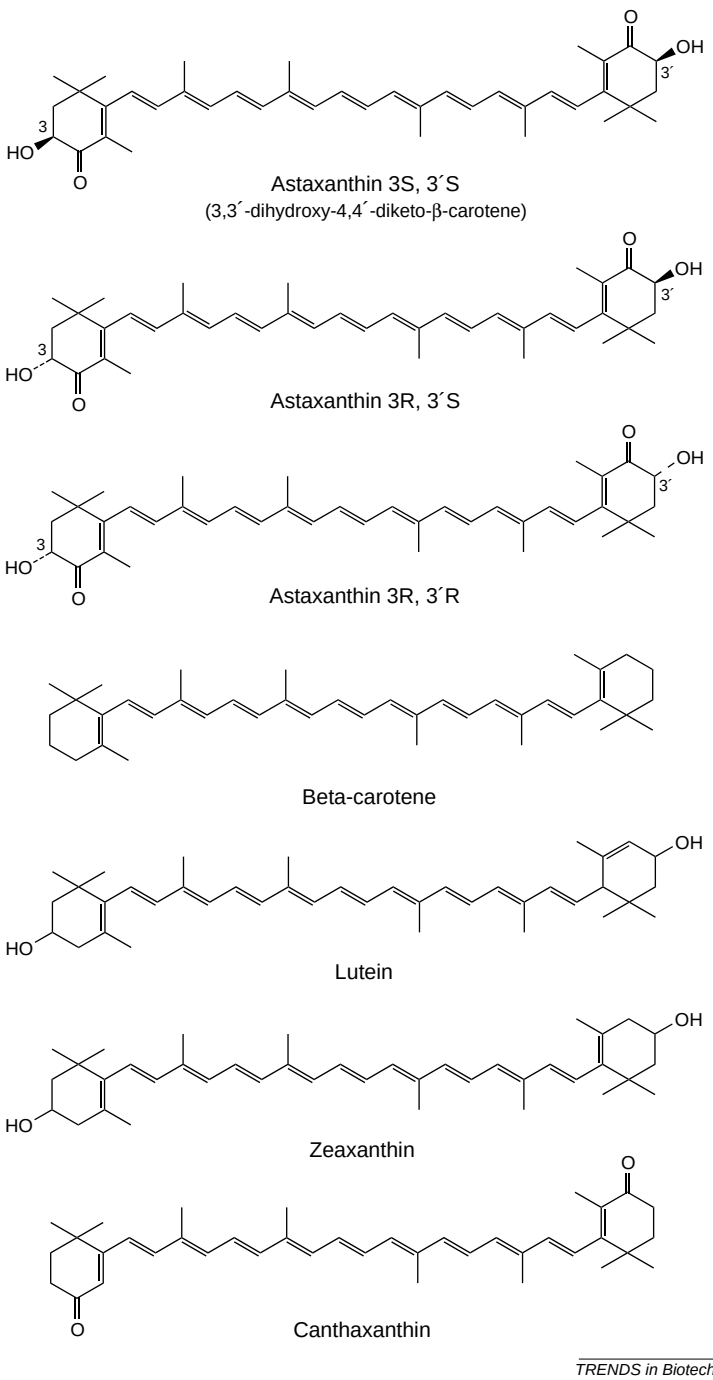

Fig. 1. Structures of selected carotenoids.

potent biological antioxidants that can absorb the excited energy of singlet oxygen onto the carotenoid chain, leading to the degradation of the carotenoid molecule but preventing other molecules or tissues from being damaged [8,9]. They can also prevent the chain reaction production of free radicals initiated by the degradation of poly-unsaturated fatty acids, which can dramatically accelerate the degradation of lipid membranes. Astaxanthin is very good at protecting membranous phospholipids and other lipids against peroxidation [10,11].

Astaxanthin's antioxidant activity has been demonstrated in several studies. In some cases, astaxanthin has up to several-fold stronger free radical antioxidant activity than vitamin E and β-carotene [12,13]. The antioxidant properties of astaxanthin are believed to have a key role in several other properties such as protection against UV-light photooxidation, inflammation, cancer, ulcer's *Helicobacterpylorii* infection, aging and age-related diseases, or the promotion of the immune response, liver function and heart, eye, joint and prostate health.

Astaxanthin as a photoprotectant

Exposure of lipids and tissues to light, especially UV-light, can lead to production of singlet oxygen and free radicals

and photo-oxidative damage of these lipids and tissues [7]. Carotenoids have an important role in nature in protecting tissues against UV-light mediated photo-oxidation and are often found in tissues directly exposed to sunlight. Astaxanthin can be significantly more effective than β-carotene and lutein at preventing UV-light photooxidation of lipids [14]. Oxidative damage to the eye and skin by UV light has been widely documented [7] and thus the unique UV protection properties of astaxanthin could be very important for eye and skin health.

Astaxanthin and eye health

Two of the leading causes of visual impairment and blindness are age-related macular degeneration (AMD) and age-related cataracts. Both diseases appear to be related to light-induced oxidative processes within the eye [7,15]. It is therefore not surprising that factors related to oxidation have been shown in epidemiological studies to be related to an elevated risk for AMD. A high dietary intake of carotenoids, specifically lutein and zeaxanthin (from spinach, kale, and other leafy green vegetables) is associated with a reduced risk for both nuclear cataracts and AMD [15–17]. Lutein and zeaxanthin, two carotenoid pigments closely related to astaxanthin, are concentrated in the macula of the eye [18].

The structure of astaxanthin is very close to that of lutein and zeaxanthin but has a stronger antioxidant activity and UV-light protection effect [14]. Astaxanthin has not been isolated in the human eye. However, an animal study [19] demonstrated that astaxanthin is capable of crossing the blood–brain barrier and, similar to lutein, will deposit in the retina of mammals. The retinal photoreceptors of rats fed astaxanthin were less damaged by a UV-light injury and recovered faster than animals not fed astaxanthin. Therefore, it can be inferred that deposition of astaxanthin in the eye could provide superior protection against UV light and oxidation of retinal tissues pointing to the potential of astaxanthin for eye health maintenance.

Astaxanthin and skin health

Excessive exposure of unprotected skin to sunlight results in sunburn and can also lead to photo-induced oxidation, inflammation, immunosuppression, aging and even carcinogenesis of skin cells. Pre-clinical studies show that typical dietary antioxidants, such as α-tocopherol, ascorbic acid or β-carotene, could reduce such damage [20–22].

Astaxanthin is believed to protect the skin and eggs of salmon against UV-light photo-oxidation [23,24]. Astaxanthin supplementation helped protect the retinal photoreceptors in the eyes of rats exposed to acute UV-light injury [19] and the *in vitro* protective effect of astaxanthin against UV-induced photooxidation [14] was stronger when compared with β-carotene and lutein. These findings suggest that astaxanthin has an excellent potential as an oral sun-protectant. Although diet supplementation with β-carotene or astaxanthin has demonstrated benefits in other types of cancer, the animal or clinical studies with these two compounds are inconclusive when it comes to skin cancer [20,25,26]. More studies are needed to better understand the possible interactions between various antioxidants and their potential prooxidative role, to determine under which conditions supplementation with carotenoids such as astaxanthin can help reduce skin carcinogenesis.

Astaxanthin and inflammation

In inflammation-related clinical conditions such as Crohn's disease, toxic reactive oxygen species (ROS) are released by phagocytic leucocytes at the site of inflammation (intestinal mucosa and lumen). These, plus increased concentrations of neutrophiles at the site of inflammation, create a pro-oxidative balance that leads to lower levels of antioxidant vitamins and increased levels of markers of oxidative stress and lipid peroxidation [27]. Furthermore, oxidants have been directly linked to the stimulation of inflammation genes in endothelial cells [28]. Similarly, ROS have been attributed an aggravating role in the inflammation that accompanies asthma [29] and exercise-induced muscle damage [30].

Astaxanthin was found to reduce induced swelling of rat paw, that vitamin E did not reduce [12]. More recently, dietary astaxanthin was found to help fight symptoms of ulcer disease from *Helicobacter pylori*. Astaxanthin reduced symptoms of gastric inflammation and was also associated with shifts in the inflammation response [31]. Although it could be assumed that the antioxidant properties of astaxanthin explains its anti-inflammatory activity, further studies are needed to better understand the specific mode of action of astaxanthin in fighting inflammation.

Astaxanthin and heart health

High blood levels of LDL-cholesterol (the 'bad' cholesterol) are associated with an increased risk of atherosclerosis. However, HDL blood levels are inversely correlated with coronary heart disease and are indicative of protection against atherosclerosis. Usually LDL in plasma is not oxidized and oxidation of LDL is believed to contribute to the development of atherosclerosis [32] thus it might be possible to reduce the risk of atherosclerosis by antioxidant supplementation. Epidemiological and clinical data indicate that dietary antioxidants might protect against cardiovascular disease [33].

Astaxanthin is carried by VLDL, LDL and HDL in the human blood. An *in vitro* test and a study with human subjects ingesting daily dosages as low as 3.6 mg astaxanthin per day for two consecutive weeks demonstrated that astaxanthin protects LDL-cholesterol against induced *in vitro* oxidation [34]. In an animal model study, astaxanthin supplementation led to an increase in blood levels of HDL [35], the form of blood cholesterol inversely correlated with coronary heart disease. Thus, astaxanthin could benefit heart health by modifying blood levels of LDL and HDL cholesterol. Finally, astaxanthin could also be beneficial to heart health by reducing inflammation presumably associated with the development of coronary heart disease [36].

Astaxanthin and cellular health

In the mitochondria, multiple oxidative chain reactions generate the energy needed by the cell but produce large

amounts of free radicals that need to be neutralized to maintain proper mitocondrial function. It is hypothesized that the cumulative oxidative damage to mitochondria is the main culprit for the senescence of cells, which in turn is responsible for aging [37]. The efficacy of astaxanthin in preventing *in vitro* peroxidation of mitochondria of rat liver cells can be as high as 100 times that of vitamin E [12]. This highlights the unique capacity of astaxanthin in helping to preserver mitochondrial functions and its unique potential in the fight against aging. Astaxanthin's superior role in protecting cellular membranes is believed to derive from its ability to protect both the inner part and external surface of membranes against oxidation (a result of the moieties of its polyene chain and terminal rings as well as of rigidifying membranes and modifying their permeability) [38–40]. Antioxidants, carotenoids in particular, are not only essential to cellular health because they help protect cellular components against oxidative damage but also because they have a role in regulating gene expression and in inducing cell-to-cell communications [41,42]. Recently, astaxanthin was reported to have a role in regulating CYP genes in rat hepatocytes, although it did not seem to have that effect in human hepatocytes [43]. Also carotenoids are active inducers of communication between cells at the cell-gap junctions (the water-filled pores in the cell membranes that permit cell-to-cell communications needed to modulate cell growth and, in particular, to limit expansion of cancerous cells) [42]. Thus, it is hypothesized that carotenoids affect DNA regulating RNA responsible for gap-junction communications and that this role in cell-gap junctions communications might explain some of the anti-cancer activities of astaxanthin.

Anti-cancer properties of astaxanthin

Several studies have demonstrated the anti-cancer activity of astaxanthin in mammals. Astaxanthin protected mice from carcinogenesis of the urinary bladder by reducing the incidence of chemically induced bladder carcinoma [44]. Rats fed a carcinogen but supplemented with astaxanthin had a significantly lower incidence of different types of cancerous growths in their mouths than rats fed only the carcinogen. The protective effect of astaxanthin was even more pronounced than that of β-carotene [45]. Furthermore, a significant ($P < 0.001$) decrease in the incidence of induced colon cancer in those rats fed astaxanthin versus those administered only the carcinogen was found [46]. Dietary astaxanthin is also effective in fighting mammary cancer by reducing growth of induced mammary tumors by $>50\%$, more so than β-carotene and canthaxanthin [47]. Astaxanthin inhibits the enzyme 5-α-reductase responsible for prostate growth and astaxanthin supplementation was proposed as a method to fight benign prostate hyperplasia and prostate cancer [48]. More recently, astaxanthin supplementation in rats was found to inhibit the stress-induced suppression of tumor-fighting natural killer cells [49]. As noted earlier, astaxanthin's anti-cancer activity might be related to the carotenoids' role in cell communications at gap junctions, which might be involved with slowing cancer-cell growth [42], the induction of xenobiotic-metabolizing enzymes [50] or by modulating immune responses against tumor cells [51].

Astaxanthin in detoxification and liver function

The liver is a complex organ in which intense catabolism and anabolism take place. Liver functions include active oxidation of lipids to produce energy, detoxification of contaminants, and destruction of pathogenic bacteria, viruses and of dead red blood cells. These functions can lead to significant release of free radicals and oxidation byproducts and therefore it is important to have mechanisms that protect liver cells against oxidative damage. Astaxanthin is much more effective than vitamin E at protecting mitochondria from rat liver cells against lipid peroxidation [12]. Astaxanthin also induces xenobiotic-metabolizing enzymes in rat liver, a process that could help prevent carcinogenesis [52]. Astaxanthin can induce xenobiotic metabolizing enzymes in the lung and kidney [50].

Astaxanthin and the immune response

Immune response cells are particularly sensitive to oxidative stress and membrane damage by free radicals because they rely heavily on cell-to-cell communications via cell membrane receptors. Furthermore, the phagocytic action of some of these cells releases free radicals that can rapidly damage these cells if they are not neutralized by antioxidants [53]. Astaxanthin significantly influences immune function in several *in vitro* and *in vivo* assays using animal models. Astaxanthin enhances *in vitro* antibody production by mouse spleen cells [54] and can also partially restore decreased humoral immune responses in old mice [55]. Other evidence also points to the immunomodulating activity of astaxanthin on the proliferation and functions of murine immunocompetent cells [56]. Finally, studies on human blood cells *in vitro* have demonstrated enhancement by astaxanthin of immunoglobulin production in response to T-dependent stimuli [57].

Astaxanthin and neurodegenerative diseases

The nervous system is rich in both unsaturated fats (which are prone to oxidation) and iron (which has strong prooxidative properties). These, together with the intense metabolic aerobic activity and rich irrigation with blood vessels found in tissues of the nervous system, make tissues particularly susceptible to oxidative damage [58]. There is substantial evidence that oxidative stress is a causative or at least ancillary factor in the pathogenesis of major neurodegenerative diseases (Alzheimer's, Huntington's, Parkinson's and amyotrophic lateral sclerosis, ALS) and that diets high in antioxidants offer the potential to lower the associated risks [59–62].

The above-mentioned study with rats fed natural astaxanthin [19] demonstrated that astaxanthin can cross the blood brain barrier in mammals and can extend its antioxidant benefits beyond that barrier. Astaxanthin, is therefore an excellent candidate for testing in Alzheimer's disease and other neurological diseases.

Safety of *Haematococcus* astaxanthin

A recent study was designed specifically to examine the effects by dietary astaxanthin on the health of humans [63]. In this study, 33 healthy adult volunteers were given natural astaxanthin supplementation over a period of 29 days. Each subject consumed daily either 3.85 mg astaxanthin (low dose) or 19.25 mg astaxanthin (high dose). Volunteers underwent a complete medical examination before, during, and at the end of the study and no ill effects or toxicity from ingestion of the astaxanthin supplement were observed. Other studies (reviewed [63]) support the conclusion that *Haematococcus* astaxanthin does not appear to possess any health risks at the tested dosages.

Haematococcus astaxanthin supplements have been available to the public for ~3 years. A recent survey of consumers of a commercial *Haematococcus* astaxanthin supplement indicates several benefits from astaxanthin supplementation. Users were asked to indicate all conditions from which they suffered, from a list of acute and chronic health conditions, and for each condition whether they had observed improvements as a result of *Haematococcus* astaxanthin supplementation. Users were also asked to compare efficacy of *Haematococcus* astaxanthin supplementation with that of well-known anti-inflammatory drugs. An improvement as a result of *Haematococcus* astaxanthin supplementation was observed in 85% of the health conditions reported (Table 1). Of 26 comparisons with popular brands of prescription drugs, *Haematococcus* astaxanthin supplementation was reported to be as effective as or more effective than the anti-inflammatory drugs in 92% of the comparisons. Of 62 comparisons with over-the-counter (OTC) drugs including aspirin or ibuprofen, astaxanthin supplementation was reported as effective or more effective in 76% of the comparisons.

Given that the possibility of placebo effect or subjective bias cannot be ruled out in that study the interpretation of these results must be taken with some caution. Nevertheless, the large percentage of responses indicating a positive effect of *Haematococcus* astaxanthin supplementation on health conditions that have or might have a strong inflammation component as well as the positive comparisons of the efficacy of the supplementation with that of anti-inflammatory drugs are indicative of strong anti-inflammatory properties for astaxanthin [12,31]. The exact mode of action and circumstances under which astaxanthin can help fight inflammation remains to be clarified, whether it is by breaking the chain formation of free radicals aggravating inflammation or through modulation of enzyme-mediated inflammation mechanisms. These survey results, however, support the unique potential of astaxanthin to be used as the nutritional component in treatment or prevention strategies against several health problems caused by oxidative stress, UV-light photooxidation or inflammation.

Production and future of *Haematococcus* astaxanthin

Commercial production of *Haematococcus* astaxanthin is very recent. Astaxanthin accumulation in *Haematococcus* is induced under stressful growth conditions. Thus, producers that use large-scale, outdoor, systems have adopted a two stage strategy whereby the first stage consists in growing *Haematococcus* biomass under conditions conducive to fast growth in enclosed photobioreactors followed by a second stage in which carotenogenesis is induced by changing the cells' environment to stress promoting conditions. Alternatively, *Haematococcus* astaxanthin can be produced indoors mixotrophically. The astaxanthin-rich cells are easily harvested by settling and centrifugation. Then, the cell biomass is cracked (to increase astaxanthin bioavailability) and dried. Finally, the dried product can be directly encapsulated or the astaxanthin extracted to be included in nutraceutical formulations [2].

Originally, *Haematococcus* astaxanthin producers attempted to enter the fish (specially salmon) feed market. However, price competition from synthetic astaxanthin ($<$US\$2000 kg^{-1}) relegated *Haematococcus* astaxanthin

Table 1. Effect of *Haematococcus* astaxanthin (AstaFactor) supplementation on chronic and acute health conditions

Health condition	Number of reports	Improves condition		Does not improve condition	
		Number	%	Number	%
Sore muscles and joints	146	128	88	18	12
Back pain	48	42	88	6	13
Cholesterol	37	29	78	8	22
Osteoarthritis	20	19	95	1	5
Prostate	15	11	73	4	27
Asthma	13	11	85	2	15
Menstrual cramps	8	6	75	2	25
Rheumatoid arthritis	7	6	86	1	14
Diabetes	5	1	20	4	80
Macular degeneration	5	3	60	2	40
Sunburn	5	5	100	0	0
Post-surgery inflammation	4	4	100	0	0
Fibromyalgia	3	3	100	0	0
Gastritis	3	3	100	0	0
Gingivitis	3	2	67	1	33
Peptic ulcers	2	2	100	0	0
Prostatitis	2	2	100	0	0
Ulcerative colitis	2	0	0	2	100
TOTAL	328	277	85	51	15

producers to supply small, specialty markets. We believe that present commercial producers cannot compete against synthetic astaxanthin on price alone. However, as production technology is optimized and production is transferred to lower cost locales, *Haematococcus* astaxanthin might compete against synthetic astaxanthin on price. Furthermore, and as the public becomes educated and demands natural pigmented salmon (and others) or regulations require the use of natural feed ingredients, *Haematococcus* astaxanthin could demand a premium price over synthetic astaxanthin, as has been the case in the vitamin E and β-carotene markets [64,65].

Alternatively, as recent research has pointed to the possible functions of astaxanthin in the human body, a market for nutraceutical astaxanthin has started to develop. Although the size of this market is closely guarded by commercial producers it is expected that it could reach a size of several hundred million US$ within 5 to 10 years.

Conclusion

Based on recently published literature we conclude that *Haematococcus* astaxanthin supplementation might be a practical and beneficial strategy in health management. This conclusion is supported by astaxanthin's strong antioxidant activity and its possible role in health conditions in several tissues in the human body and by the results of a user survey. As consumers become aware of the putative benefits of *Haematococcus* astaxanthin supplementation, and as commercial production is optimized and costs lowered, the perceived market potential for *Haematococcus* astaxanthin will be realized.

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