(43)

Natural Healing Track

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Astaxanthin

Continuing Education Module

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ASTAXANTHIN

Continuing Education Module

by Timothy J. Maher, Ph.D.

NEW HOPE INSTITUTE OF RETAILING

Goal:

The goal of this module is to introduce the reader to the carotenoid astaxanthin and examine its antioxidant actions especially as it relates to potential therapeutic approaches in addressing cardiovascular disease, neurodegenerative disease, cancer, immune function status and visual health.

Objectives:

Following successful completion of this module, the participant will be able to:

- describe the unique antioxidant features of the carotenoid astaxanthin;
- list the sources in nature and the functions of astaxanthin in animals that produce and consume astaxanthin;
- explain findings of recent research that describe the effects of astaxanthin in cardiovascular disease, neurodegenerative disease, visual health, cancer and immune system function;
- describe the pharmacokinetics of astaxanthin and list its potential side effects.

Oxygen and Antioxidants

As aerobic organisms we depend completely on molecular oxygen for our existence; just a few minutes without oxygen usually results in irreversible damage or death. Our friendly atmosphere usually provides ample oxygen via the air we breathe, and even a relatively small decrease in the air's oxygen content has noticeable effects. For instance, when traveling from sea level to high altitudes where the oxygen content is slightly lower, most individuals will find tasks requiring even minimal exertion much more difficult. Even highly trained athletes will find performance in their events a greater challenge at high altitudes.

Although oxygen is absolutely critical for life, this molecule also has a dark side to its actions. Oxygen is found in a large number of harmful by-products that are constantly being produced and defended against by healthy organisms. These so-called reactive-oxygen species (ROS) contain reduced oxygen molecules including free radicals such as the superoxide, hydroxyl and peroxyl radicals and non-radicals such as ozone, lipid peroxides, hydrogen peroxide, and singlet oxygen.[1] Additionally, a number of nitrogen compounds containing oxygen, such as nitric oxide and peroxynitrite, also are extremely harmful. Many of these compounds are so highly energetic that they react almost instantly with many neighboring molecules such as proteins, DNA, RNA, carbohydrates and lipids. The consequence of such oxidative attack may include protein oxidation, DNA and RNA damage, and lipid peroxidation. Even small alterations to some of these basic molecules of life would be expected to have dire consequences.

This constant attack against the body, known as oxidative stress, is continuously countered by mechanisms designed to neutralize such damage and prevent diseases that might be associated with such insult (Table 1). While certain repair enzymes can sometimes reverse the damage produced by the ROS, the ability of antioxidants to neutralize the ROS prior to inducing damage is an extremely important defense mechanism that helps to support a healthy existence and most likely prevents disease.[2,3] During the last decade there has been a tremendous amount of interest in the roles ROS and oxidative stress might play in the development and progression of a number of neurodegenerative diseases including Alzheimer's, amyotrophic lateral sclerosis (Lou Gerhig's) and Parkinson's diseases, as well as macular degeneration. Many other diseases such as atherosclerosis, cataracts, cancer, cerebrovascular disorders, multiple sclerosis, bacterial and viral meningitis, and epilepsy have also been suggested to involve an underlying oxidative insult.[4] The rate at which many of the processes of aging occur have also been attributed by some to reactions involving oxidative stress. Because antioxidants are capable of scavenging harmful ROS and reducing overall oxidative

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Table 1

Conditions Likely to be Associated with Oxidative Stress
• Aging • Alzheimer's Disease • Artherosclerosis • Bacterial Meningitis • Cancer • Cataracts • Cerebrovascular Diseases • Epilepsy • Lou Gehrig's Disease (Amyotrophic Lateral Sclerosis) • Macular Degeneration • Parkinson's Disease • Viral Meningitis

stress, it is not surprising that there has been much interest in investigating the use of such compounds to slow the progression of, and in some cases even prevent, a wide array of diseases.

Cartenoids and Astaxanthin

Of the antioxidants investigated for their potential health benefits, the carotenoids have received the most attention. These lipid-soluble pigments from plants, algae and some bacterial species, comprise well over 700 compounds that account for the beautiful red, orange and yellow colors observed in many of these lower species. While most higher animals are unable to endogenously synthesize these carotenoids, they do accumulate them via ingested foods. In many aquatic and land species the spectacular coloration observed results from the mixture of such carotenoids. Besides their obvious function of providing pigmentation for many species, the carotenoids also serve a multitude of important chemical functions such as their ability to absorb light, quench singlet oxygen, be oxidized and isomerize, bind to hydrophobic surfaces, and solubilize in organic media.[5] However, not all carotenoids are equal, and the differences in activities of the individual carotenoids are thought to result from the uniqueness of their chemical structures.

While the most notable carotenoid is the vitamin A precursor, β–carotene, one carotenoid that has received much attention lately is astaxanthin (3,3'-dihydroxy-β-β-carotene-4,4'-dione). Chemically, astaxanthin is classified as a xanthophyll, which is a family of carotenoids with specific substitutions on the benzoid rings. While there are three possible isomers of astaxanthin, only one exists naturally (the S,S' configuration). Lower organisms synthesize astaxanthin beginning with acetyl CoA and proceeding through a number of important intermediates including phytoene, lycopene, β–carotene and canthaxanthin. Both astaxanthin and canthaxanthin are examples of conjugated keto-carotenoids, and both are further classified as xanthophylls. While β–carotene is a vitamin A precursor, astaxanthin cannot be converted to this vitamin and thus cannot support retinol-specific processes.

Astaxanthin provides the rich pink color observed in various aquatic species including the salmonids (e.g., salmon) and crustaceans (e.g., crabs, lobster, shrimp), and even some nonaquatic species such as the flamingo (whose diet includes some astaxanthin-producing organisms). The carotenoids found in phytoplankton, algae and plants normally participate in those organisms' photosynthetic processes by acting as secondary light-absorbing molecules. Salmonids and flamingos don't actually produce astaxanthin but instead obtain it from other animals they consume. The richest source of astaxanthin by far is the algae *Haemococcus pluvialis*, which is used commercially as a feed additive to provide color to "farm-raised" salmon and other fish (Table 2).

The astaxanthin that is contained in living lobsters is complexed with proteins called carotenoproteins that actually imparts a bluish-brown color to these animals. However, when the carotenoproteins are denatured, as occurs during the high temperatures associated with cooking, the astaxanthin is liberated and the bright red coloration results.[6] Besides providing the coloration to such fish, and thus enhancing their economic value (e.g., few people would find white salmon attractive), some recent studies have indicated a "vitamin-like" role for astaxanthin in these fish.

Experimentally, the potency or capacity of an antioxidant to chemically neutralize or scavenge harmful oxygen- or nitrogen-reactive compounds can be determined routinely in the laboratory. One such assay measures the production of ROS-induced lipid peroxides in test tubes in the absence and in the presence of various concentrations of a suspected antioxidant. In such *in vitro* assays, astaxanthin has been shown to be typically at least 10 times more potent than the other standard carotenoids such as canthaxanthin, β–carotene, lutein, lycopene, tunaxanthin and zeaxanthin.[7,8] When compared with α–tocopherol (vitamin E), astaxanthin's potency as an antioxidant ranges from approximately 80 times to as much as 550 times greater.[9,10] Additionally, when tested against a wide array of ROS and nitrogen-reactive species, astaxanthin appears to be the most effective in scavenging this wide variety of harmful products. Astaxanthin is thought to be able to span the lipid/protein bilayer of biological membranes, imparting a powerful antioxidant effect. Astaxanthin's combination of superior potency and versatility yield the ideal antioxidant. Therefore, it is not surprising to find that this carotenoid has been studied for its potential utility in a number of disease states in humans and disease models in animals.

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Anti-cancer Activity and Astaxanthin

The anti-cancer activity of carotenoids and related compounds has been the focus of much attention since epidemiological reports of an association between low

Table 2

SOURCES AND CONTENT OF ASTAXANTHIN	
Source	Content (mg/kg)
Salmon	
Sockeye	26-37
Coho	9-21
Chum	3-8
Chinok	8-9
Atlantic	3-11
Red Seabream	2-14
Rainbow Trout	1-13
Krill	46-130
Krill Oil	727
Crayfish Meal	137
Yeast(*Pfaffia r.*)	30-800
Haematococcus pluvialis	10,000-30,000

levels of certain carotenoids and various types of cancers. Some of the cancers studied with respect to the carotenoid association include lung, esophageal, stomach, colon, rectal, prostate, breast, cervical, ovarian, endometrial, bladder and skin. For instance, while men with the lowest plasma β–carotene levels had an increased risk of prostate cancer, when supplemented with carotenoids (especially lycopene) their risk decreased by 36%. Carotenoids may be of benefit in the prevention or the amelioration of cancers via their ability to scavenge ROS, inhibit the growth of certain tumors, inhibit malignant transformation, enhance immune function, and upregulate certain genes (e.g., connexin 43). Astaxanthin, with its potent antioxidant activity and its beneficial immune actions, might be predicted to be especially active in a number of animal models of cancer.

The anti-cancer activities of astaxanthin, canthaxanthin and β–carotene against the growth of mammary tumors in young mice were determined.[11] For three weeks animals were fed either 0, 0.1, or 0.4 percent in the diet of the individual carotenoid prior to inoculation with a fixed amount of tumor cells. Astaxanthin dose-dependently inhibited growth of the tumor cells, and was the most effective of the various carotenoids tested. Additionally, while canthaxanthin and β–carotene failed to alter lipid peroxidation activity in the tumors, astaxanthin was highly effective in this regard. Similar protective effects of astaxanthin were found in a mouse model of urinary bladder carcinogenesis.[12] Astaxanthin has also been reported to be effective against a number of other carcinogenic stimuli including aflatoxin, chloroform, viruses, and 4-nitroquinoline-1-oxide.[13,14] A recent proposed mechanism for astaxanthin in influencing the pathways associated with cancer involves the ability of this carotenoid to enhance membrane stabilization and promote the synthesis of the gene for the gap-junction protein, connexin-43. Alterations in this protein would be expected to beneficially influence cell-to-cell communication and increase the likelihood of the maintenance of cellular homeostasis and thus normal function.

Cardiovascular Health

Within the last decade there have been many reports in the literature that document a beneficial effect of various carotenoids in the cardiovascular system. Much attention has been centered on the influence of these substances on the levels of cholesterol as contained in the form of various lipoproteins. Most studies have documented a positive correlation between levels of the atherogenic low-density lipoproteins (LDL) and the prevalence of diseases of the cardiovascular system (e.g., hypertension, angina pectoris, myocardial infarction). In contrast, it is generally recognized that an inverse correlation exists between high-density lipoproteins (HDL) and the incidence of cardiovascular health. A beneficial lipoprotein profile is one characterized by low levels of the cholesterol-rich LDL ("bad-cholesterol") with high levels of HDL ("good-cholesterol").

While there have been many studies in humans and in animals with the more common carotenoids and other antioxidants, few studies have been performed with astaxanthin. One study reported a significant increase in HDL levels when rats were treated with astaxanthin in the diet.[15] In this same study, administration of another carotenoid, β–carotene, was without effect on HDL. This study provides evidence of yet another difference in the activities of individual carotenoids. Obviously there is a need for well designed (e.g., double-blind, randomized) clinical studies in humans to determine if a similar beneficial effect on lipoprotein profiles will be realized.

"Within the last decade there have been many reports in the literature that document a beneficial effect of various carotenoids in the cardiovascular system."

Immune Function and Astaxanthin

Many studies have demonstrated the ability of astaxanthin to enhance antibody responses and augment humoral immune functions. In a recent study using mice treated with *H. pylori*, astaxanthin was found to significantly reduce bacterial load and gastric inflammation, while also being able to modulate cytokine release in splenocytes harvested from these treated animals.[16] Interestingly, in this study astaxanthin was found to shift the observed T-lymphocyte response from a predominantly T-helper–1 (TH-1) cell response dominated by interferon–γ (INF–γ), to a mixed TH-1/TH-2 response with involvement of both INF–γ and interleukin-4 (IL-4). In this particular animal model, INF–γ is most likely involved with mediating the gastric damage and irritation observed in the gastrointestinal tract. On the other hand, the IL-4 is thought to be involved with the repair of the gastric mucosa. This was the first demonstration in the literature of a compound causing a shift from the usual abundance of cytokines that normally mediate the damage associated with infection to one characterized by a greater amount of protective cytokines. Further studies comparing the utility of astaxanthin and β–carotene to enhance antibody responses in splenocytes in a T-cell dependent fashion, demonstrate that the former is effective while the latter is ineffective.[17]

Astaxanthin has been tested in a preliminary human study utilizing *H.pylori*-positive patients. When administered five times per day for three weeks (8 mg doses), astaxanthin significantly decreased gastritis in all subjects, even though they remained positive for *H. pylori*. Although there is just one preliminary human study reported thus far; based on the multitude of animal studies reported in the literature there has been much excitement regarding the potential utility of this versatile and potent carotenoid in the overall therapy of *H. pylori* infection in humans.

Visual Health

The carotenoids play an essential role in the physiological function and overall health of the eye in those animals that have vision. Most of the information regarding the role of carotenoids in the visual system has focused on β–carotene and its metabolic by-product vitamin A.

> "In preliminary animal experiments the protective effects of astaxanthin in preventing damage to the visual system has been reported."

However, more information has recently appeared that documents the importance of the antioxidant role of a number of carotenoid and noncarotenoid compounds in the eye. In order for a particular antioxidant to function in the eye, that compound must traverse the blood-retinal barrier. The blood-retinal barrier is similar in its function and structure to the blood-brain barrier, about which we know much more. This specialized structure, which helps to prevent the unhindered passage of compounds into the central nervous system from the periphery, regulates which compounds will pass. Of the carotenoids examined, astaxanthin appears to easily penetrate the central nervous system, a characteristic not typically seen with all carotenoids or antioxidants. Since the molecular weight of astaxanthin is under 600 daltons, and the molecule is very lipophilic, one would expect this compound to pass the blood-brain barrier with relative ease. Thus, for any antioxidant to produce a beneficial effect on visual health it is imperative that that compound be able to enter the central compartment of interest.

Table 3

CHARACTERISTICS OF ASTAXANTHIN

- Extremely potent antioxidant
- Very versatile at scavenging various ROS
- Unique immune modulatory activity
- Effective against a number of cancer promoters
- Enhances gap junctions & cell communication
- Cardioprotective / lipoprotein - beneficial
- Easily enters the central nervous system
- Protects against photic-induced injury
- No toxicity reported to date

The eye is a complex structure that has been extensively studied from a chemical as well as a physical perspective. One of the most important structures that comes in contact with photic stimuli is the retina. Within the retina, in its most central portion, resides the macula, a dense accumulation of photoreceptor cells (e.g., rods and cones), which function to convert incoming light into nerve impulses. Our sharpest vision occurs at the very center of the macula in an area known as the fovea. This is where the highest concentration of photoreceptor cells are located. In addition to their role in participating in the visual process by absorbing light to produce images, the carotenoids also function to protect the retina from damage. The incoming light may contain highly energetic photons from blue and purple light, which can produce high levels of harmful ROS and cause damage to the photoreceptor cells if not adequately protected. The exposure to such energetic photons can cause lipid peroxidation due to the high concentration of polyunsaturated fatty acids in the macula's photoreceptive membranes, in addition to other photo-oxidative damage. Normally, the use of sun glasses can help to prevent some of this harmful exposure and minimize damage.

In some avian species (e.g., shore birds like the kingfisher) there is a very high density of astaxanthin found in the fovea, while in others (e.g., land-based birds) there appears to be very little, if any. This unique distribution of astaxanthin in the foveal cone oil droplets of such shore birds is believed to serve two functions: 1) to enhance their air:water interface visual acuity, and 2) to protect the retina from the harmful effects of glare off the water. These birds have been studied extensively and support the potential utility of antioxidants that do enter the eye as visual protective agents.

In preliminary animal experiments the protective effects of astaxanthin in preventing damage to the visual system has been reported. Following intraperitoneal administration of vehicle or astaxanthin (37.5 mg/kg), rats were exposed to 200 foot-candles of green-filtered fluorescent light at 490-580 nm for 24 hours. The thickness of the outer nuclear layer of the retina was then determined as a decrease in the thickness of this layer is associated with photic injury. While rats treated with vehicle had significant damage to the retina as evidenced by an approximate 35 percent decrease in the thickness of the outer nuclear layer, those treated with astaxanthin had only a 6 percent decrease in thickness. Another study demonstrated the ability of astaxanthin to prevent the depletion of rhodopsin levels in the retina following a similar photic insult.

Some diseases of the eye, especially involving the retina, may involve degeneration due to exposure to harmful photic stimuli. While genetic factors probably play a significant role in a number of these disorders, the role of oxidative stress susceptibility is now thought to be an underlying mechanism in the damage observed. In humans macular degeneration is a general term used when describing a number of diseases of the retina. The most prevalent type is the "dry" type, which is characterized by the formation of small yellow deposits under the macula known as drusen. These drusen are eventually associated with a thinning and drying out of the macula, and a subsequent impairment of visual acuity.

In one human study there was reported to be an inverse relationship between the production of certain size drusen and the intake of provitamin A and dietary vitamin E.[18] Because this study determined intake of these vitamins by using food frequency questionaires, some of the findings were not robust enough to make clear recommendations regarding the role of these particular antioxidants and visual health. For instance, this study failed to demonstrate a significant relation between intake of these antioxidants and the progression of maculopathy, probably also due to the small number of patients in this study who developed the late stages of maculopathy. In another study involving a review of the epidemiological literature on the association of nutritional antioxidants (vitamin C, vitamin E, carotenoids) and the progression of maculopathy, the authors concluded that such antioxidants are likely to delay the onset of age-related vision impairments.[19] Much interest was expressed regarding the potential protective effects to be afforded by supplementation with the xanthophylls. However, not all xanthophylls might be appropriate for these types of studies, since a previous report has indicated the ability of canthaxanthin to concentrate in the eye and cause lens opacities. No such reports have appeared for astaxanthin, and importantly, the body does not appear to be able to convert canthaxanthin to astaxanthin. It is clear that there is a need for more carefully controlled, double-blind, large studies in the future to conclusively determine the effectiveness of astaxanthin and other antioxidants in promoting visual health.

"Because astaxanthin appears to enter the central nervous system better than many other antioxidants, its utility in many central disorders should hold significant promise."

Toxicity and Pharmacokinetics of Astaxanthin

To date there have been no reports of serious adverse effects associated with the administration of astaxanthin to animals. Attempts have been made to determine the lethal dose –50 but fail to find a dose that will adversely affect the animals. Even when the upper limit of 8 grams of astaxanthin per kilogram of animal body weight are administered for 10 days, no toxicity has been noted. There is a good likelihood that similar findings will be observed in humans. The doses of astaxanthin that have been suggested are on the order of 2-4 mg per day.

A recent report regarding the absorption and distribution of astaxanthin demonstrated that following oral administration of 100 mg to human volunteers, peak astaxanthin levels in plasma (1.24 mg/L) occurred at six hours. In this study, most of the astaxanthin was associated with the very low density lipoprotein, with some also associated with the HDL and LDL fractions. While this was an acute study, it will be important to study the distribution and metabolism of astaxanthin in chronic administration studies because this will more closely mimic the situation associated with the usual use of astaxanthin.

Summary

While not well known by many healthcare providers at the present time, astaxanthin is a potent xanthophyll antioxidant that may have several advantages over other better-known carotenoids in a wide variety of disease states including neurodegenerative diseases, cancer, immune disorders, cardiovascular disease and visual health (Table 3). The ability of astaxanthin to scavenge a wide variety of free radicals and other ROS, and its potency compared to other traditional, better-known antioxidants, makes it an attractive choice for future studies. Additionally, because astaxanthin appears to enter the central nervous system better than many other antioxidants, its utility in many central disorders should hold significant promise. To date there has been no toxicity reported with this potent antioxidant carotenoid.

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Astaxanthin
Continuing Education Test Questions

Natural Healing Track

August 2000

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Directions : Select your answer and check *one* best answer for each of the test questions. When you have answered all of the questions, please print or type all requested information and mail your completed test, along with processing fee, to the appropriate address listed below.

1. The highest concentration of astaxanthin based on weight is found in:
   - a.flamingo meat.
   - b.crustaceans such as lobsters.
   - c. the algae *Haematococcus pluvialis.*
   - d.sockeye salmon.

2. Reactive oxygen species (ROS):
   - a. only react with lipids but not DNA and RNA.
   - b. are only produced under anaerobic conditions.
   - c. are slow to react.
   - d.include hydrogen peroxide and hydroxyl radicals.

3. Astaxanthin:
   - a.is classified as a carotenoid.
   - b.is classified as a xanthophyll.
   - c.has antioxidant properties.
   - d.all of the above are correct.

4. Astaxanthin:
   - a.can be synthesized by mammals.
   - b.is used to provide color to farm-raised salmon.
   - c.is a very water soluble compound.
   - d. can be converted to vitamin A.

5. Which of the following has the greatest antioxidant capacity when tested *in vitro* in a lipid peroxidation assay?
   - a. tocopherol (vitamin E.)
   - b. β–carotene.
   - c. lycopene.
   - d.astaxanthin.

6. Excessive oxidative stress has been suggested to be linked to which of the following?
   - a. aging
   - b.cancer
   - c. macular degeneration
   - d.all of the above are correct

7. Astaxanthin treatment has been demonstrated to do which of the following?
   - a. increase the bacterial load in animals inoculated with *H. pylori*
   - b. decrease HDL lipoprotein levels
   - c. increase LDL lipoprotein levels
   - d.none of the above are correct

8. Carotenoids:
   - a.may be useful in decreasing the incidence of prostate cancers.
   - b.all cross the blood-brain barrier equally well.
   - c. are all converted to vitamin A.
   - d.are all equally safe for human consumption.

9. The responses in the immune system to astaxanthin treatment may include:
   - a.a shifting from TH-1 responses (which are gastric irritation promoting) to TH-2 (which are gastric repairing).
   - b.increased gastric inflammation.
   - c.a thinning of the outer nuclear layer
   - d.all of the above

10. Astaxanthin has been demonstrated to possess which of the following activities?
    - a.anticarcinogenic
    - b.protective against photic injury.
    - c.cardioprotective.
    - d.all of the above are correct.

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Haematococcus astaxanthin: applications for human health and nutrition

Martin Guerin, Mark E. Huntley and Miguel Olaizola

Mera Pharmaceuticals Inc., 73–4460 Queen Kaahumanu Hwy, Suite 110, Kailua-Kona, Hawaii 96740, USA

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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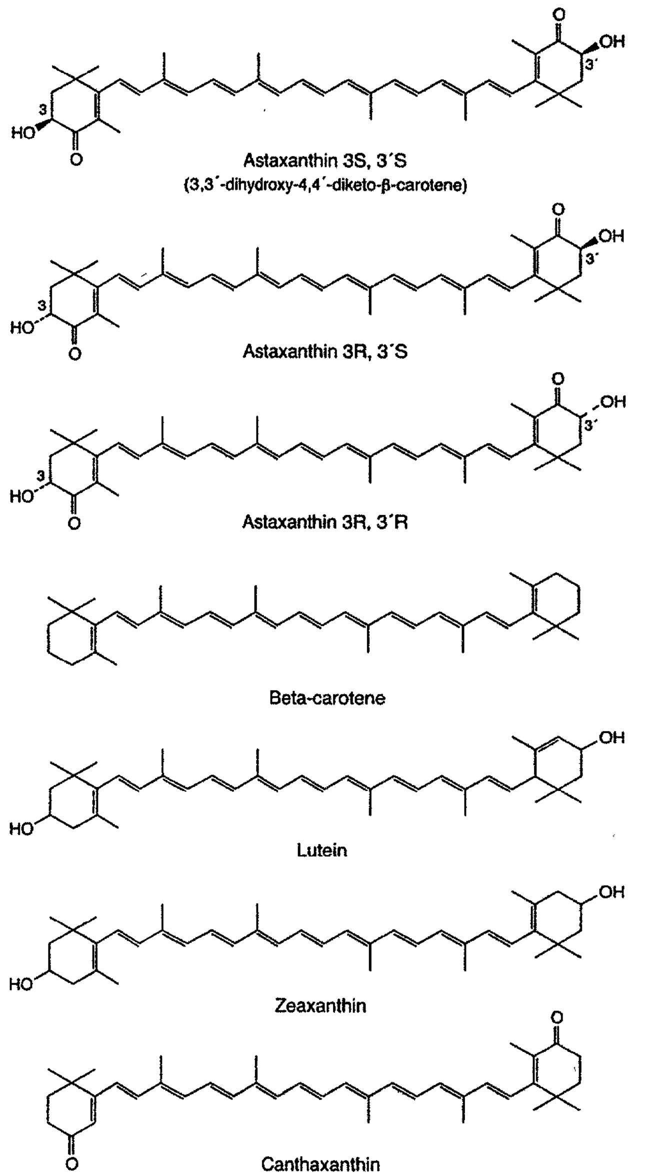

Fig. 1. Structures of selected carotenoids.

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 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.

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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