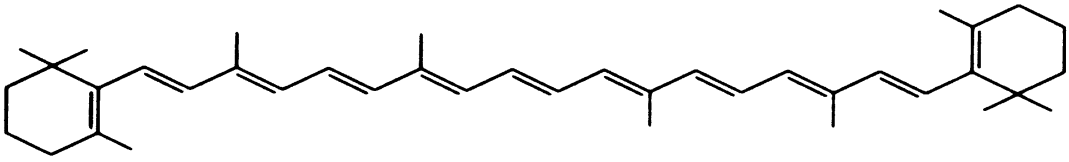
BioAstin, Nature's Premier Astaxanthin Source

What are carotenoids?

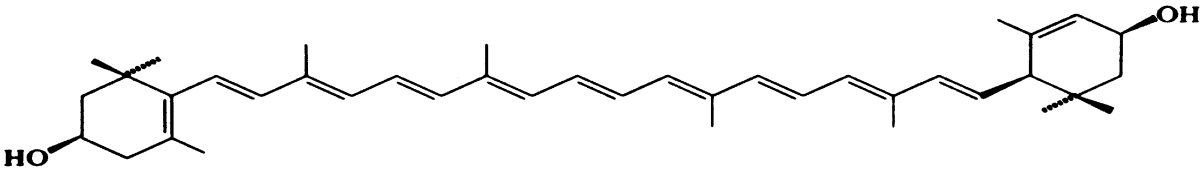
Carotenoids are a family of about 700 fat-soluble molecules that are only produced by phytoplankton, algae, plants, and a limited number of fungi and bacteria. Beta-carotene was named after its isolation from carrots and is probably the most familiar carotenoid. It is categorized as a 'carotene' whereas other carotenoids with additional oxygenated groups, such as lutein, are 'xanthophyll' (ZAN-tho-fill) carotenoids.

premier

β-Carotene



Lutein

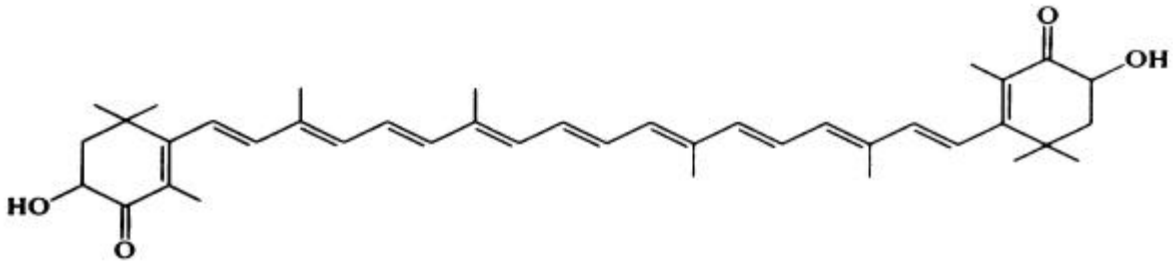


Carotenoids are all around us and account for the wide variety of colors in nature. Most often, we see them in the brilliant yellow and red colors of fruits, vegetables, and leaves. In plants and algae, carotenoids are a vital participant in the photosynthetic process along with chlorophyll and other light-harvesting pigments.

While some animals are able to alter carotenoids into other forms, they cannot synthesize them so they must be obtained from their diet. The pink flamingo, for instance, filters *Spirulina* or other algae from bodies of water and metabolically converts the yellow carotenoids, beta-carotene and zeaxanthin, into the pinkish-red carotenoids, astaxanthin and canthaxanthin. These red carotenoids are deposited into the feathers and elicit the striking color of this bird. Numerous species of bird, crustaceans, fish and insects are also pigmented with carotenoids obtained from their diet.

Humans have come to rely on and harness the broad range of activities from carotenoids. This is evidenced by the conversion of from beta-carotene to vitamin A or the protection provided by lutein and zeaxanthin in the macula region of the eye against UV light damage. Carotenoids also act as important antioxidants against the damaging effects of free radicals and singlet oxygen that occur during normal cellular function.

Where does astaxanthin fit in?



Astaxanthin (asta-ZAN-thin) is the king of the carotenoid family. Compared to beta-carotene, it has two additional oxygenated groups on each ring structure that gives it a deep red color and crowns it as the elite xanthophyll. These extra functional groups give astaxanthin extraordinary antioxidant capability and properties unlike other carotenoids. Astaxanthin also acts as a cell stabilizer, playing the role of rivets between membranes.

Astaxanthin was first isolated and identified from lobsters in 1938. Since that time it has been found in a diverse array of animals such as birds, shrimp, crabs, crawfish, sea bream, plants and nearly all Salmon (Coho, Atlantic, pink, chum, Chinook, and trout). It's not new, astaxanthin has been in our diet for thousands of years. But until now, only those of us who eat large quantities of salmon, caviar or other seafood have been able to reap the benefits of astaxanthin. If you ever have the opportunity to walk around an Asian fish market you will be awestruck by a sea of red astaxanthin!

(Japanese fish market, Tokyo)

Interestingly, animals have adapted to exploit the potent antioxidant properties of astaxanthin. One familiar example is seen with salmon that instinctively migrate thousands of miles to spawn in their native grounds. Salmon accumulate astaxanthin from their diet and then deposit it in their muscle tissue which accounts for 65% of body mass. Mother Nature chose astaxanthin to protect their fatty acids and other sensitive cellular components from oxidative stress during this extremely traumatic and aerobic migratory event. We recognize this as the healthy pinkish-red glow in the flesh of salmon and trout.

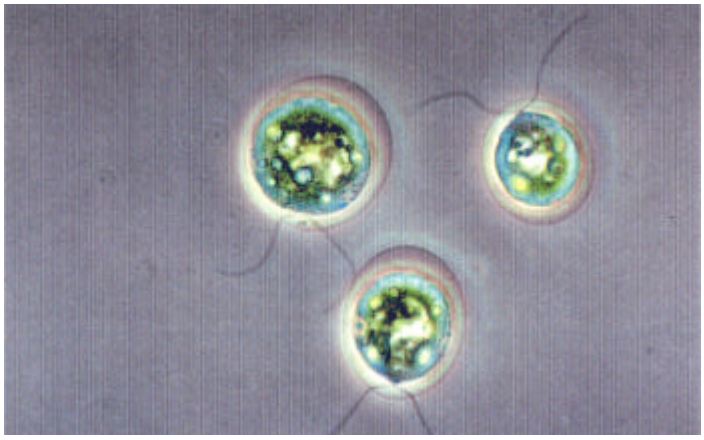
(Carpaccio of salmon containing astaxanthin from NatuRose)

To start the cycle again, female salmon lay astaxanthin-laden eggs to protect the eggs against UV light and an oxidative environment thereby allowing the best chance of survival for the next generation. In fact, Atlantic salmon juveniles require astaxanthin as a vitamin to grow and thrive normally.

(Newly hatched salmon 'alevins' with astaxanthin-laden yolk sacs)

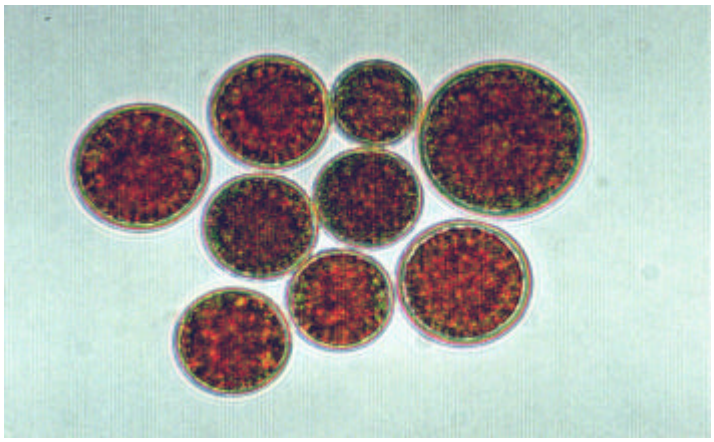
Sources of Astaxanthin

Microscopic *Haematococcus* (ha-mato-kok-us) algae is nature's richest source of astaxanthin and is found world-wide in small pools of fresh water. During favorable conditions, the algae is green and motile, seeking out nutrient-rich pockets in these small pools of water.



(Green & motile *Haematococcus* algae 400x magnification)

When nutrients are depleted or the pool dries up, the cells begin to go into a 'hibernation phase' and produce massive amounts of astaxanthin as protection against UV light and oxidation. When the cells have finished encysting, they can contain from 1.5% to 4 % (15,000-40,000 ppm) astaxanthin by dry weight. Encysted cells can lay dormant for many years until favorable conditions occur and the cells once again 'germinate' into green motile cells. It is likely that you may have seen *Haematococcus* algae as a dark red crust in birdbaths or old rock quarries. The name of the algae was actually derived from the ancient Greek words meaning 'blood-seed' (haem and coccus).



(Encysted *Haematococcus* algae containing astaxanthin 400x magnification)

Another source of astaxanthin is the yeast, *Phaffia*, which can sometimes be found growing on the bark of certain trees. By comparison, *Phaffia* yeast from nature produces about 200-400 ppm of astaxanthin. Commercial strains have been genetically modified to increase the astaxanthin up to 8000 ppm, still only a fraction of the concentration that *Haematococcus* naturally produces. Krill oil is another possible source, but it has an offensive 'fishy' odor, contains only about 1200 ppm and is considered a limited resource. Synthetic astaxanthin is also produced by some companies through complex chemical reactions, however it is not the same form as found in nature.

Astaxanthin has a long history of use in the human diet from consumption of seafood such as salmon and shrimp. A recent study conducted by the US Food and Drug Administration assessed the astaxanthin concentration in a large variety of wild salmon species. This survey showed that the average astaxanthin concentrations ranged from about 5-40 ppm of flesh.

Species	**Astaxanthin range**	**Astaxanthin average**
Sockeye salmon	30-58 mg/kg	40.4 mg/kg
Coho salmon	9-28 mg/kg	13.8 mg/kg
Pink salmon	3-7 mg/kg	5.4 mg/kg
Chum salmon	1-8 mg/kg	5.6 mg/kg
Chinook king salmon	1-22 mg/kg	8.9 mg/kg
Atlantic salmon	5-7 mg/kg	5.3 mg/kg

Oxidative Stress

Humans have a sophisticated circulatory system to deliver and regulate oxygen-rich blood to every cell of the body. Although oxygen is required for normal metabolic activity, it also can present severe challenges to cells. Harmful forms of oxygen such as singlet oxygen or free radicals are commonly formed as a result of photooxidation, physiological stress and normal immune system functions. These highly unstable free radical molecules contain unpaired electrons that rob electrons from other molecules and thereby cause cellular injury such as lipid oxidation, protein degradation, and DNA damage. Free radicals also have an inordinate affinity to attack unsaturated fatty acids, the principle component of cell membranes. These peroxidized fatty acids then create more fatty acid radicals in a chain reaction.

A number of theories suggest that an upset oxidative balance can be a contributing factor in such conditions as rheumatoid arthritis, heart disease, Parkinson's disease, Alzheimer's disease, cancer and stroke. Our bodies normally have a balance of free radicals and an arsenal of antioxidants to counter them, such as superoxide dismutase, catalase, and an assortment of peroxidase enzymes. However, a host of conditions such as poor nutrition, chemical exposure, stress, air pollution, smoking, ultraviolet light or disease can upset this equilibrium.

Even strenuous physical exercise leads to an increase in reactive oxygen and nitrogen species that causes oxidative stress and free radical damage to cells. Enzymatic and non-enzymatic antioxidant systems play a vital role in protecting tissues from excessive oxidative damage during exercise. However, depletion of the antioxidant systems may induce a state wherein the defenses of tissues are overwhelmed by excess

radical molecules and are then vulnerable to damage. Reactive oxygen and nitrogen species formed during strenuous exercise can cause skeletal muscle damage, inflammation, and lipid peroxidation as well as a contributing factor in the loss of calcium within cells after strenuous exercise. Thus, researchers recommend the use of dietary antioxidants to combat free radical damage to muscles.

What is BioAstinÔ ?

It is now evident that the antioxidant potential of carotenoids can significantly reduce free radicals and oxidative stress to help the body maintain a healthy state. Until recently, there hasn't been a concentrated form of astaxanthin available as a dietary supplement. However, after significant technological advances, *Haematococcus* algae is now cultured in the pristine environment of Hawaii by Cyanotech Corporation. *Haematococcus* algae harnesses sunlight for energy to grow and reproduce, and fresh water from the mountain aquifer is used in a series of culture systems designed to produce high concentrations of astaxanthin, naturally.

(Culture system for *Haematococcus* algae)

The algae is harvested, dried and milled into a fine powder to ensure maximum bioavailability of the astaxanthin. The powder is then carefully formulated into food grade safflower oil, and gelcaps are manufactured to contain 2 milligrams of astaxanthin per dose.

Why safflower oil? Recent research suggests that the proper ratio of fatty acids in oils may be the most helpful way of reducing the risk of heart disease. High oleic safflower oil is relatively rich in monosaturated fatty acids that appear to lower LDL (bad cholesterol) levels without changing HDL (good cholesterol) in the blood. The very low concentration of saturates together with enough essential polyunsaturates provide the healthiest combination. Since this oil is virtually identical in fatty acid composition to olive oil, it has sometimes been used as an excellent blending partner for this classic oil.

Typical Fatty Acid Composition of High Oleic Safflower Oil

Palmitic	5.0%
Stearic	2.0%
Oleic	77.0%
Linoleic	15.0%
Others	1.0%

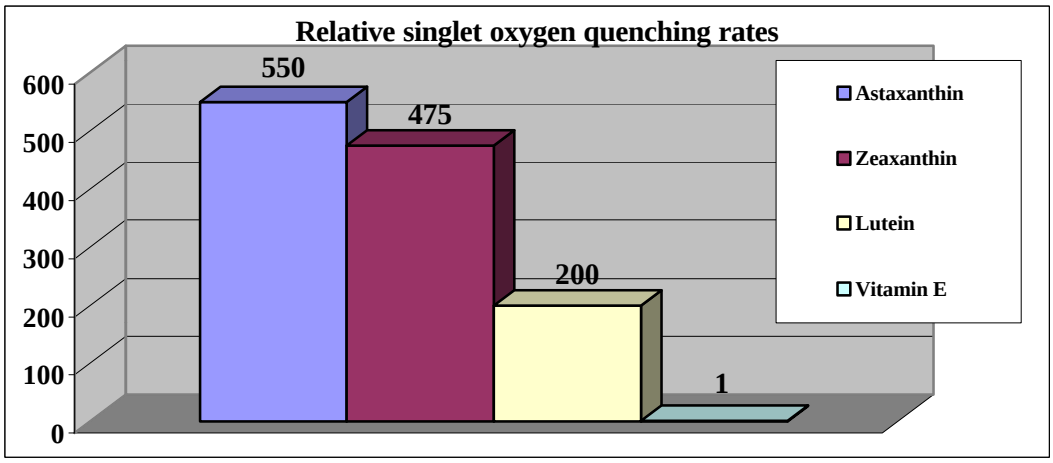
The *Haematococcus* strain used for BioAstin was collected from the wild and has never been genetically modified. It produces high amounts of astaxanthin just as Mother Nature intended. The Food and Drug Administration cleared BioAstin for marketing in August 1999 based on substantial documentation, manufacturing and safety information. There has never been any safety concerns arising from astaxanthin or *Haematococcus* algae. The recommended dosage is 2 milligrams of astaxanthin per day, which is contained in 1 gelcap. This is equivalent to about 400 grams of Atlantic salmon!

Benefits of Astaxanthin

Nature's Most Potent Carotenoid Antioxidant

Carotenoids, and especially astaxanthin, protect cells against oxidation by 1) quenching singlet oxygen and dissipating the energy as heat and 2) scavenging free radicals to prevent and terminate chain reactions. Due to its particular molecular structure, astaxanthin has both a very potent neutralizing effect against singlet oxygen as well as a powerful scavenging ability for free radicals. Therefore astaxanthin serves as an extremely effective antioxidant against these harmful molecules. Astaxanthin is 550 times more effective against singlet oxygen than vitamin E and significantly better than other carotenoids tested. One prominent researcher has proposed astaxanthin as the 'Super Vitamin E'.

(Adapted from Shimidzu, 1996)



Eye and Central Nervous System Protection

A number of studies have shown carotenoids to be essential for proper health of the eye in that they protect the retina against oxidative damage. The macula is the small central part of the retina encompassing an area of about 2 millimeters in diameter directly behind the lens of the eye. Interestingly, this specialized macular region only occurs in higher primates such as monkeys and man. It consists primarily of cones, which are responsible for color discrimination, and is the region that produces the sharp vision needed to read and see fine details clearly. The photoreceptor cells contain the highest concentration of polyunsaturated fatty acids (PUFA's) of any tissue in the human body and a particularly high level of oxygen that renders it very susceptible to lipid peroxidation. Thus, when high-energy blue light waves interact with the retina, singlet oxygen and other excited oxygen species are formed through photooxidation causing peroxide damage to the lipids. The cumulative oxidative damage then lead to the degenerative changes seen in the ageing macula.

Carotenoids within the macula are perfectly suited to absorb high-energy blue light and act as an antioxidant to quench damaging oxygen species. It is generally agreed that the blue region of the light spectrum (400-500 nm) damages the retina by the creation of excited oxygen species, principally singlet oxygen in the eye. Clinical studies have indicated that light injury is a major cause of a disease called "age-related macular degeneration" (AMD) because of this cumulative light insult. AMD results in a gradual loss of photoreceptor cells and is the leading cause of irreversible blindness among older Americans that have decreased levels of carotenoids in their eyes. It has been shown that a higher dietary intake of carotenoids is associated with a 43% lower risk of AMD.

Unlike beta-carotene, astaxanthin is able to readily cross the blood-brain barrier and protect the retina against photo oxidation and loss of photoreceptor cells. The brain, spinal cord and nerves are also particularly abundant in unsaturated fatty acids. The relatively high metabolic activity and oxygen demand of these tissues makes them vulnerable to oxidative damage. Due to its unique property of crossing the blood-brain barrier, astaxanthin has the additional capability to protect the brain, nerves and spinal

cord from damage caused by oxidative injury. There is one US patent issued to the University of Illinois for the use of astaxanthin to treat AMD.

Ultraviolet Light Protection

Ultraviolet radiation (UVR) has long been known to cause skin damage and certain cancers. Exposure of the skin to UVR triggers a chain reaction within skin cells that generates lipid peroxides and other high-energy free radicals. These molecules can then damage proteins or even DNA and increase the risk of skin cancer. Although the body utilizes an array of antioxidants such as vitamin E, vitamin C, selenium, catalase (CAT) and superoxide dismutase (SOD) to scavenge these free radicals, they can become quickly depleted under the severe stress of UVR exposure. Initial studies with astaxanthin show that it may complement the body's antioxidant defenses and help reduce damage.

In cell cultures, addition of astaxanthin exhibits superior protection against UVR light-induced oxidative stress compared to lutein and beta-carotene. Cell cultures were grown in differing concentrations of carotenoid-supplemented media, exposed to UVR light for four hours, and then various stress indicators were measured such a thiobarbituric acid reactive substances (TBARS). Without carotenoids in the media, catalase (CAT) and superoxide dismutase (SOD) were significantly decreased following the UVR exposure, whereas TBARS were significantly increased. However, addition of carotenoids to the cultures was found to protect these enzymes. Astaxanthin was 20 times more effective than lutein and 200 times more effective than beta-carotene in protecting against UVR-induced loss of catalase. Similarly, astaxanthin was 100 times more effective than beta-carotene and 200 times more effective than lutein defending against loss of superoxide dismutase activity. Supplementation with astaxanthin was 100-fold more effective than lutein and 1000-fold more effective than lutein at preventing UVR-induced increase in TBARS. The researchers propose that carotenoids other than beta-carotene, and particularly astaxanthin, may be key biological antioxidants against UVR-induced damage. Other studies show that astaxanthin exerts a specific action on transglutaminase enzymes that help consume harmful polyamines in response to skin irradiation.

Prevention of sunburn should be the most important goal, but often this cannot be avoided. Sunscreens have assumed a major component of primary prevention, however, numerous BioAstin consumers have reported that they are able to endure a longer exposure to sunlight without sunburns. Some users who regularly get sun blisters due to their occupational requirements in the sun, claim their condition was significantly improved after taking BioAstin for 2 weeks. Those with extreme sensitivity to sunlight state that they attained a significantly higher tolerance to exposure. Cyanotech is sponsoring clinical trials in 2000 to investigate these beneficial effects of BioAstin in protecting against UVR damage.

Metabolic Effects of Astaxanthin

Carpal Tunnel Syndrome (CTS) is an ailment caused by excess pressure of the median nerve in the wrist resulting in numbness, tingling, and pain in the arm, hand, and fingers. Usually, carpal tunnel syndrome is considered an inflammatory disorder caused

by repetitive stress, physical injury, or other conditions that cause the tissues around the median nerve to become swollen. It occurs either when the protective lining of the tendons within the carpal tunnel become inflamed and swell or when the ligament that forms the roof becomes thicker and broader. Compression on the median nerve fibers by the swollen tendons and thickened ligament slows down the transmission of nerve signals through the carpal tunnel.

Users of BioAstin afflicted with CTS have reported a complete recovery from this debilitating affliction. It appears that the powerful antioxidant capacity of astaxanthin in conjunction with immune modulation may result in a potent anti-inflammatory response that alleviates the painful symptoms of carpal tunnel syndrome. To that end, Cyanotech has initiated carefully controlled clinical trials with leading experts to determine if these observations may have a positive benefit on a wider population of carpal tunnel sufferers. Results of the study are expected to be complete by December 2000.

Astaxanthin may also have physiological benefits in exercise metabolism. A double-blind study in Sweden was conducted in which 40 healthy students were divided into two groups for a series of physiological tests with and without astaxanthin supplementation from *Haematococcus* algae. At the end of six months, there was a significant difference in the strength/endurance that was measured by knee bends and a barbell weight. The results showed the placebo group attained an average score of only 35% that of the experimental group that had consumed astaxanthin.

High-density lipoprotein (HDL) is a complex of lipids and proteins that functions as a transporter of cholesterol in the blood. Higher levels of HDL "good cholesterol" and lower levels of LDL "bad cholesterol" are associated with a decreased risk of atherosclerosis and coronary heart disease. One published study showed that rats fed dietary astaxanthin for 30 days increased their HDL cholesterol over 14 mg/dL compared to those without astaxanthin. Conversely, the LDL bad cholesterol decreased from the control diet of 12.5 mg/dL to 9.6 mg/dL when supplemented with astaxanthin. Neither beta-carotene nor canthaxanthin elicited the same effect. Additional studies are in progress, but it is speculated that astaxanthin or other carotenoids can also decrease the oxidation of these lipid-carriers and thereby reduce the risk of atherosclerosis.

Cancer Deterrence

Anticarcinogenic effects of carotenoids are likely partly attributable to their antioxidant effect, in that high-energy radicals are related to the process of cancer initiation and propagation. Secondly, modulation of the immune response by astaxanthin appears to play a role in the positive effects observed with cancer.

Typically, various carcinogens are used to induce specific cancers in animals and supplements are added or left out of their diet to test the effects. In rats, carcinogens have been used to induce colon cancer and study the effect of assorted anticancer agents. In one study, rats were exposed to 3 weekly injections of a carcinogen and then fed diets with or without astaxanthin at 100 and 500 ppm for a further 34 weeks. At the end of the 37-week study, 63% of the chemically induced group had cancerous intestinal neoplasms. However, the chemically induced group that was subsequently treated with 100-ppm astaxanthin had an incidence of only 41%. Groups treated with 500 ppm of dietary astaxanthin had a significantly reduced cancer rate of only 31%. The researchers state

the results clearly indicated that administration of astaxanthin after exposure to the carcinogen significantly inhibited colon carcinogenesis as the astaxanthin concentration increased. They speculate that the significant antitumor properties of astaxanthin may be partly due to its ability to suppress cancer cell growth as well as an enhanced immune response.

In another study, mice were given a chemical carcinogen in drinking water for 20 weeks and then water with 50 ppm astaxanthin was administered for 20 more weeks. At the end of the 41-week study, the chemically induced control mice had a 42% incidence of bladder carcinomas. However, the chemically induced mice that were post-treated with 50-ppm astaxanthin had a significantly lower rate of only 18% bladder carcinomas. The researchers suggest that astaxanthin is a possible chemopreventive agent for bladder carcinogenesis and such an effect is partly due to antioxidant effects and suppression of cancer cell proliferation.

Researchers have also given rats 20 ppm of a carcinogen in drinking water for 8 weeks to induce oral cancer. The animals were fed diets with and without 100 ppm astaxanthin either during or after the induction phase. At the end of the 32-week study, the incidences of tongue squamous cell carcinomas were 54% in the non-treated control group, while both groups treated with astaxanthin had none. The researchers state that the results clearly indicate that dietary administration of astaxanthin significantly depressed the development of the chemically induced tongue neoplasms either during the chemical insult or subsequently. The researchers again speculate that the inhibitory effects of astaxanthin may be partly due to its suppression of cancer cell growth and enhanced immune response.

In one cancer trial, mice were fed synthetic diets containing 0, 0.1, or 0.4% beta-carotene, canthaxanthin or astaxanthin for three weeks. Their mammary fat pad was then injected with tumor cells to determine the anticancer activities of the carotenoids. After 66 days of feeding, the concentration of astaxanthin in the plasma was 135-145 fold higher than that of beta-carotene and 4-6 fold higher than that of canthaxanthin at both doses. By the end of the study, all mice had tumors but they varied in size considerably. Final tumor weights of the unsupplemented mice (1.9 grams) were similar to those groups fed beta-carotene at the two dosages (1.8 and 2.1 grams). Mice fed canthaxanthin had tumor weights of 1.3 and 1.5 grams for the two diets, respectively. However, mice supplemented with astaxanthin had the lowest tumor weights of 1.2 and 1.0 gram for the two diets. Final tumor volume in mice fed astaxanthin was 50-60% smaller than that of the control mice. Dietary astaxanthin inhibited mammary tumor growth as the concentration increased in the diet, whereas this effect was not observed with beta-carotene or canthaxanthin.

In an applied study, mice were fed a carcinogen to induce stomach tumors and subsequently fed various concentrations of astaxanthin-enriched egg yolks. Those fed the astaxanthin-rich egg yolks developed only one third as many tumors per animal. The authors conclude that astaxanthin-enriched egg yolks inhibited tumorigenesis of the mouse forestomach induced by the carcinogen.

Some researchers speculate that increased expression of a gene called “connexin43” which lets cells communicate to slow or stop cell division when “crowding takes place (as in a tumor) may explain some of the the suppressing effects of astaxanthin in carcinogenesis.

Immune Support

Singlet oxygen is toxic to the immune system because it can promote the production of free radicals, which in turn can damage white blood cells and reduce their ability to fight invading organisms. Prolonged stress as a result of excessive exercise can lead to a decline in certain aspects of immune system function such as natural killer cell activity of some antibodies. Even free radicals generated by the oxidative stress of prolonged intense exercise have been shown to impair immune function and lead to an inflammatory response and may last from 3 to 72 hours. Epidemiological studies have demonstrated a correlation between carotenoid intake and the increased resistance to viral, bacterial, fungal and parasitic infections. Studies have indicated that the mechanism for this protective attribute is at least partially due to the direct enhancement of the immune response by carotenoids as well as an antioxidant adjuvant to the bodies own artillery.

Carotenoids have been shown to enhance both the non-specific and specific immune system and protect cell membranes and cellular DNA from mutation. Carotenoids have a significant stimulatory effect on the immune system, as seen by the proliferative antibody response in mice studies. Astaxanthin augments the release of immune weapons such as interleukin-1 alpha and tumor necrosis factor alpha in mice greater than canthaxanthin and beta-carotene. The conclusion of one study was that astaxanthin had the best cytokine-inducing activity and may provide a beneficial immunomodulating role.

In a number of cell culture studies, astaxanthin at very low concentrations significantly enhanced the production of IgM antibodies whereas other carotenoids (zeaxanthin, lutein, lycopene, and canthaxanthin) did not have the same effect. Astaxanthin was also the only carotenoid to significantly increase the number of IgG antibody-secreting cells. The researchers conclude that astaxanthin has a significant enhancing action on antibody production when cells are presented with antigens. The importance of these studies is that at the initial stage of an infection, a particular bacteria or virus may be too low to elicit an effective immune reaction, and astaxanthin appears to enhance the response.

Helicobacter pylori is a bacteria that colonizes the human gut, causing type B gastritis, peptic ulcer disease and gastric cancer. In the United States, *Helicobacter* affects about 20% of persons below the age of 40 years, and 50% of those above the age of 60 years. The seriousness of these gastric diseases is partially caused by the body's own immunological response to the *Helicobacter* bacteria. Upon infection in the gastric mucus membrane, a chain of events leads to the activation phagocytic cells that contribute to mucosal inflammation and damage. A recent study demonstrated that mice infected with *H. pylori* and then treated with *Haematococcus* algae showed a significantly decreased bacterial load and decreased inflammation in the stomach. Treatment of the infected mice with a *Haematococcus* algae extract reduced the average bacterial load by four-fold and the gastric inflammation score by 35%. These positive results were attributed to a shift in the immune system response as well as the neutralization of reactive oxygen metabolites that encourages the inflammation.

Other studies indicate a significant immunomodulating action of astaxanthin in that carotenoid supplementation may be beneficial in restoring immune responses in

older animals. Furthermore, it was speculated that dietary carotenoids could reduce the chance of developing autoimmunity and malignancies by enhancing T-helper cell functions and promoting specific antibody responses.

Safety Studies with Haematococcus Algae and Astaxanthin

Haematococcus algae has never been associated with any toxicity in the reported literature or in field studies. Numerous animal and human studies have proven its safety. *Haematococcus* algae has been reviewed by the US Food and Drug Administration and cleared for marketing as a new dietary ingredient by means of the Dietary Supplement Health and Education Act. It is also been approved in Japan for use in both foods and animal feeds. A different formulation of *Haematococcus* algae has already gained wide acceptance in the aquaculture markets as a pigmentation and vitamin source for salmon, trout, shrimp and ornamental fish and has been approved as a feed additive for salmonids by the Canadian Food Inspection Agency and the US Food and Drug Administration. Similar registrations are in progress in the European Union and other countries.

A number of standard toxicity and safety studies have been conducted with *Haematococcus* algae. Acute oral toxicity and chronic oral toxicity studies have been conducted on rats and mice with a dosage levels as high as 18 grams of *Haematococcus* algae per kg of body weight. Animals were evaluated for mortality, pharmacotoxic signs, and body weights. No visible abnormalities were observed, nor differences in body weights during the studies. The postmortem examinations did not reveal any abnormalities in the organs at the end of the studies.

Mutagenicity tests under standard conditions are negative for *Haematococcus* algae. A published study with rats fed 400 ppm astaxanthin for 41 days showed no harmful effects on body/organ weight, enzyme activities, pregnancy, or litter size.

For a more detailed review of astaxanthin, please refer to BioAstin Technical Bulletin "axbul62.pdf".

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