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Algal Astaxanthin – A potent molecule for good health.

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Abstract

Astaxanthin is a naturally occurring molecule found in many classes of Algae and the most abundant carotenoid in the marine world. Astaxanthin can be found in many of seafood such as salmon, trout, sea bream and shrimps. Astaxanthin cannot be synthesized by animals and must be provided in the diet. The main or richest commercial source for natural astaxanthin is *Haematococcus pluvialis* microalgae. During the last decade a large number of research articles and patents have been published regarding astaxanthin. Astaxanthin is a small lipid soluble molecule that can cross the blood brain and retina barriers easily. Because of its powerful antioxidant properties, astaxanthin was found to have benefits on various health conditions including inflammation, diabetics, certain cardiovascular, vision and CNS conditions. Most manufacturers have the advanced biotechnology process to cultivate large amount of enriched algae cells without the disadvantages of open pond algae systems such as problems associated with contaminations and salinity. In addition, *the Haematococcus* microalga is cultivated in ideal environmental conditions using the natural sun light as the energy source all year round.

Key words: Astaxanthin, Algae, Health, Carotenoid, *Haematococcus*

Introduction

A lesser-known carotenoid called Astaxanthin is now believed to be the most beneficial antioxidant nature has to offer. Astaxanthin is a red pigment molecule that is a member of the carotenoid family found in certain marine/fresh water algae. When eaten by shrimp and crustaceans, the pigment lends its reddish hue to their shells. As astaxanthin makes its way up the food chain, the color becomes still more concentrated, creating the beautiful reds and pinks we see in fish such as salmon and in marine birds like flamingos. Researchers have sought to explore the use of astaxanthin as a topical sunscreen because of its powerful ultraviolet light-absorbing properties. They soon found, however, that astaxanthin has many other additional benefits.

Currently, the primary natural source for astaxanthin is the microalgae *Haematococcus pluvialis*. This is the form used in the overwhelming majority of human nutritional supplements, and it is the form on which all human clinical trials have been done (Oshima *et al*., 1993). These human clinical trials have shown benefits in the areas of anti-inflammatory, cardiovascular health, eye and brain health, skin improvement and the protection of skin from UV damage. Additionally, there have been studies showing improvement in endurance and strength as well as other applications for athletes. Other sources of astaxanthin such as synthetic astaxanthin from petrochemicals and astaxanthin derived from genetically mutated phaffia yeast have never been proven beneficial in human health and have not been proven safe for direct human consumption (Kurashige *et al*., 1990).

In January 2014, a trade association of the three primary producers of astaxanthin derived *from Haematococcus pluvialis* microalgae Cyanotech Corporation, Algatechnologies and Fuji Health Science called the Natural Algae Astaxanthin Association (NAXA) was formed to promote awareness of natural astaxanthin from algae's health benefits and to distinguish between the different sources of astaxanthin. *Haematococcus pluvialis* seems to accumulate the highest levels of astaxanthin in nature. Commercially more than 40 g of astaxanthin can be obtained from one kg of dry biomass.(Spiller and Dewell, 2003) It has the advantage of the population doubling every week, which means scaling up is not an issue. However, it does require some expertise to grow the algae with high astaxanthin content. Specifically, the microalga is grown in two phases. First, in the green phase, the cells are given an abundance of nutrients to promote proliferation of the cells. In the subsequent red phase, the cells are

deprived of nutrients and subjected to intense sunlight to induce encystment (carotogenesis), during which the cells produce high levels of astaxanthin as a protective mechanism against the environmental stress. The cells, with their high concentrations of astaxanthin, are then harvested.

Recent scientific findings indicate that astaxanthin is a powerful antioxidant and can serve as a potent free-radical scavenger. Moreover, astaxanthin has been found to provide many essential biological functions, including protection against lipid-membrane peroxidation of essential polyunsaturated fatty acids and proteins, DNA damage and UV light effects; it also plays an important role in immunological defense. Oxygen is necessary for the metabolic production of energy in our bodies. Mitochondria, through the electron-transport chain, use oxygen to oxidize certain molecules and generate energy in the form of ATP. During this process, oxygen is reduced to water, producing several oxygen-derived free radicals or reactive oxygen species (ROS) which play an important role in various diseases. Normally, oxygen free radicals are neutralized by natural antioxidants such as vitamin E, or enzymes such as superoxide dismutase (SOD). However, ROS become a problem when either a decrease in their removal or their overproduction occurs, resulting in oxidative stress. This stress, and the resultant damage, has been implicated in many diseases, and a wealth of preventative drugs and treatments are currently being studied. Astaxanthin has been shown to have beneficial effects, as described in numerous medical articles, patents and excellent reviews (Lorenz and Cysewski, 2000; Guerin *et al*., 2003,) over the last 10 years.

Demand for Astaxanthin:

In recent years, there has been a growing trend toward using natural ingredients in all forms of food nutrients, resulting from increasing concerns for consumer safety and regulatory issues over the introduction of synthetic chemicals into the human food chain. This is also true for the nutraceutical and cosmetic markets. The demand for natural astaxanthin is now emerging in the multi-billion dollar nutraceutical market, and increasingly, medical researchers believe that astaxanthin may have significant pharmaceutical applications. While only a negligible part of today's market, the demand for such applications is expected to grow significantly in the near term as a result of numerous medical studies performed during the last 5 years in the area of astaxanthin applications. More and more research supports the conviction that a daily dose of ~5 mg of astaxanthin is of tremendous importance for health management, by protecting cells and body tissues from the oxidative stress caused by free radicals, among others.

Astaxanthin producers have conducted several studies in recent years to demonstrate the safety of natural astaxanthin derived *from Haematococcus* (Spiller and Dewell, 2003). A randomized, double-blind, placebo-controlled, 8-week trial designed to determine the safety of astaxanthin in 35 healthy adults was published recently . Results revealed that healthy adults can safely consume 6 mg of astaxanthin per day from *Haematococcus pluvialis* algal extract. Based on recent findings, we believe that a daily dose of astaxanthin will have an important influence in preventing a broad array of age related diseases. Moreover, small daily doses of may prevent or delay the onset of some diseases, thus saving society significant sums of money.

Health benefits of Astaxanthin:

Powerful Antioxident:

Astaxanthin's powerful antioxidant activity has been demonstrated in numerous studies showing the detrimental effects of free-radical-induced oxidative stress (Naguib, 2000) and its potential to target many important health conditions. In terms of antioxidant power or potency, astaxanthin is 550 times stronger than vitamin E, and 6,000 times stronger than vitamin C. Recent studies have shown enhanced immune response and decreased DNA damage in human subjects following Astaxanthin administration (Chew and Park, 2003). Astaxanthin is capable of crossing the blood-brain barrier in mammals (Tso and Lam 1996), a unique and important property in the realm of antioxidants. This characteristic allows Astaxanthin to extend its superior antioxidant activity to the central nervous system, which, being rich in unsaturated fatty acids is highly susceptible to oxidative damage by ROS Facchinetti *et al*., 1998). The efficacy of astaxanthin in limiting the damage produced by ROS-induced oxidative stress and improving health parameters in the tissues and the body was demonstrated in a series of *in-vitro* experiments, in pre-clinical studies and in human models.

Effect on diabetes related obesity:

Astaxanthin may have benefits on diabetic patients. Oxidative stress induced by hyperglycemia possibly causes the dysfunction of pancreatic beta-cells and various forms of tissue damage in patients with diabetes mellitus. Astaxanthin elicited beneficial effects on the progressive destruction of pancreatic beta-cells in db/db mice-a well-known obese model of type 2 diabetes. (Uchiyama *et al*., 2002). Astaxanthin was also found to have a protective effect on endothelial dysfunction of aortas in diabetic rats and the possible molecular mechanism involved. Diabetes and obesity are so closely intertwined that scientists now speak of them together as one entity, diabesity. Diabesity is a major component of metabolic syndrome. Astaxanthin holds multiple benefits in managing diabesity, with its resulting oxidative stress, high levels of chronic inflammation, and extensive tissue damage from protein and lipid glycation. In addition to preventing the main elements of diabesity, astaxanthin helps alleviate the long-term consequences faced by diabetics. Studies show that astaxanthin supplementation slows the development of diabetic nephropathy (kidney disease), reduces cataract formation and diabetic retinopathy (both preventable forms of blindness in diabetics), and reduces the many cardiovascular complications of diabesity (Yoshida *et al*., 2004).

Improve and protect cardiovascular health.

In humans and animals, astaxanthin is known to help normalize lipid profiles, reducing triglyceride and cholesterol levels while boosting beneficial HDL-cholesterol. These effects reduce the risk of clot formation within a major blood vessel (Murillo 1992, Iwamoto *et al*., 2001; Zang *et al*., 1991). Astaxanthin health benefits may also include helping men who have high cholesterol. A double-blind, placebo-controlled study conducted with overweight and obese adults found that supplementation with astaxanthin "has positive effects on improving LDL cholesterol (the so-called "bad" cholesterol), ApoB, (a substance that attaches to LDL cholesterol and transports it through the body and is a measure of cardiac risk), and oxidative stress biomarkers (Choi *et al*., 2011). Astaxanthin also reduces inflammation and decreases the production of certain enzymes that destabilize plaques and make them vulnerable to rupture which blocks blood flow. People with cardiovascular disease are at risk for vascular dementia, a form of cognitive decline caused by decreased brain blood flow and damage to cerebral vessels. Astaxanthin supplements in animals reduce the rate of complications such as strokes, and improve cognitive performance, allowing the animals to live more vigorous and active lives. In one of the most recent studies of astaxanthin and cardiovascular health, scientists reported that astaxanthin has demonstrated to be a potential antioxidant and anti-inflammatory therapeutic agent in models of CVD (cardiovascular disease).They pointed out that astaxanthin has not shown any adverse effects in human clinical trials. They predicted that because of its greater antioxidant potency and membrane preservation, astaxanthin will reduce measures of oxidative stress and inflammation and provide vascular benefits (Riccioni *et al*., 2011).

Astaxanthin health benefits also come into play for healthy aging. A 2011 study noted that astaxanthin reduced oxidative stress in overweight and obese individuals, lowered triglycerides, raised levels of "good" high-density lipoprotein (HDL) cholesterol, improved cognition, blocked DNA damage, and lowered levels of inflammation-causing substances. All of these actions are measures of aging. The authors concluded that astaxanthin's clinical success extends beyond protection against oxidative stress and inflammation, to demonstrable promise for slowing age-related functional decline (Kidd, 2011).

Slows down brain aging:

The nervous system is rich in both unsaturated fats (which are prone to oxidation) and iron (which has strong pro oxidative 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 (Facchinetti, *et al* 1998). 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 (Grant, 1997;. Borlongan, *et al*., 1996; de Rijk, 1997; Ferrante *et al*., 1997).The above-mentioned study with rats fed natural astaxanthin (Tso and Lam, 1996) 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.

Astaxanthin exerts multiple beneficial effects in the brain. Unlike many other antioxidant molecules, astaxanthin crosses the blood-brain barrier, allowing it to saturate and protect brain tissue. These features have led experts to label astaxanthin a natural brain food. Astaxanthin also directly combats the oxidative impact of abnormal proteins in both Alzheimer's and Parkinson's diseases. A human study has determined that doses of astaxanthin as high as 20 mg once daily for 4 weeks are free of side effects and suggested that the supplement was effective for age-related decline in cognitive and psychomotor functions. 12 mg/day astaxanthin improved cognitive health and learning scores in a study of healthy middle-aged and elderly subjects with age-related forgetfulness.

Major eye health stimulator:

Astaxanthin has been found to prevent or slow three of the most common eye diseases: age-related macular degeneration, cataracts, and glaucoma. The human retina naturally contains the carotenoids lutein and zeaxanthin, molecules closely related to astaxanthin. Supplementing these three carotenoids (astaxanthin 4 mg/day, lutein 10 mg/day, zeaxanthin 1 mg/day) has been shown to improve visual acuity and contrast detection in people with early age-related macular degeneration. In laboratory studies, astaxanthin supplementation protects retinal cells against oxidative stress and significantly reduces the area of destructive new blood vessel growth on retinas, a hallmark of advanced macular degeneration. Studies of patients with age-related macular degeneration reveal significant improvements in retinal electrical outputs following supplementation with astaxanthin and other carotenoids (Tso and Lam, 1996; Snodderly, 1995; Ohgami *et al*., 2003; O'Connor and O'Brian, 1998).

Glaucoma, an increase in the pressure of fluid inside the eyeball, eventually results in retinal cell death from oxidant damage and loss of blood flow. Astaxanthin restores retinal parameters to normal in eyes with experimentally-induced glaucoma. Carotenoids are present in high concentrations in the macula, an area of the retina that is responsible for central, high resolution. Research examining astaxanthin health benefits on the macula and vision problems such as macular degeneration have shown that the antioxidant can be positive. In particular, two groups of patients were assigned to receive either lutein, zeaxanthin, astaxanthin and antioxidants/vitamins or no supplements for two years. After two years, patients in the treatment group had significantly better visual acuity and improved contrast sensitivity than patients who did not take the supplement (Piermarocchi *et al*., 2012).

Early stage cancer prevention:

Astaxanthin is as effective as alpha-tocopherol in inhibiting radical-initiated lipid peroxidation in rat liver microsomes. In this system, beta-carotene appears to be a much less potent antioxidant (Palozza and Krinsky, 1992). In another study, large unilamellar liposomes comprising of egg yolk phosphatidylcholine was exposed to photo irradiation in the presence of photosensitizers. Without sensitizers, astaxanthin decreased the process much slower than beta-carotene, lycopene, and alpha-carotene. (Oshima *et al*., 1993), Research also shows that astaxanthin is an immunomodulator, astaxanthin enhances in vitro antibody production to sheep red blood cells in normal B6 mice. (Jyonouchi *et al*., 1993). Because of its immunomodulatory and anti-oxidative activities, astaxanthin may offer benefits to patients suffered from cancers. Epidemiological studies reveal that dietary intake of astaxanthin along with other carotenoids is associated with the reduced risk of many different types of cancer. Increased intake of carotenoids such as astaxanthin typically lowers cancer risk. Unlike many pharmaceuticals already being used, astaxanthin shows beneficial effects against cancer at each stage of its development. An association between astaxanthin health benefits and cancer is still in the early investigative stages. A mouse study found that astaxanthin at various doses added to the diet of mice had an effect on colitis and colitis-related colon cancer. Specifically, the authors noted that astaxanthin is one of the candidates for prevention of colitis and inflammation-associated colon cancer in humans (Yasui *et al*., 2011).

Boosts Immune system:

Studies demonstrate that astaxanthin helps balance the immune system by stimulating its infection- and cancer-fighting components while also helps to suppress the overactive immune responses that create needless inflammation. Human studies reveal astaxanthin's beneficial actions on the over-activated immune system in patients with allergies and asthma. When astaxanthin (along with ginkgo extract) was applied to white blood cells from asthmatic patients, it suppressed reactive cell

activation as well as or better than the antihistamine drugs cetirizine and azelastin. A subsequent study showed that combining these compounds with the drugs resulted in improved antihistamine activity. Astaxanthin may benefit user's immune system by enhancing antibody production. Astaxanthin enhanced in vitro antibody production to sheep red blood cells in normal B6 mice (Jyonouchi *et al*., 1993). When the actions of carotenoids were tested in normal strains of mice, astaxanthin enhanced *in vitro* antibody production to T cell-dependent antigen. And, astaxanthin exerted maximum enhancing actions when it was present at the initial period of antigen priming (Jyonouchi *et al*., 1993).

Potent Skin Protector

Even though astaxanthin is widely distributed through most organs in the body, it accumulates in the skin, where it makes its way into all skin layers (topical sunscreens can reach only the outermost layers). This can provide potent protection against ultraviolet radiation, the most powerful environmental risk factor for skin cancer. Recent studies show that astaxanthin can rejuvenate skin from within. Astaxanthin is among the most powerful and versatile marine plant antioxidants known, and as such, it has the ability to scavenge skin-damaging free radicals (O'Connor and O'Brien, 1998; Lyons and O'Brien, 2002; Savoure *et al*., 1995; Seki *et al*., 2001; Yamashita *et al*., 1995; Yamashita, 2006; Tominaga, *et al*., 2009 a, b.; Tominaga, *et al*., 2012). Human studies demonstrate that 6 mg/day of astaxanthin for 6-8 weeks reduces crow's feet wrinkles, water loss, and age spot size while enhancing moisture content, elasticity, and skin texture in both men and women, particularly when combined with topical astaxanthin application.

Benign Prostatic Hyperplasia

A study examined the effect of astaxanthin on levels of dihydrotestosterone (DHT), testosterone, and estradiol. These three hormones can have a role in the development of an enlarged prostate (benign prostatic hyperplasia, BPH) and/or prostate cancer as well as andropause (male menopause). Investigators gave a supplement that contained both astaxanthin and saw palmetto berry extract (Alphastat®) to 42 healthy men ages 37 to 70: one group took 800 mg/day while the other took 2,000 mg daily for 14 days. Analysis showed a significant increase in testosterone and a significant decrease in DHT in both groups within three days of treatment. A significant decline in estradiol was seen only in the 2,000 mg per day group. Since there was no significant difference between the increase in testosterone and decline in dihydrotestosterone between the two different doses, the authors concluded that the lower dose was sufficient for having a positive impact on these two factors (Angwafor and Anderson, 2008; Anderson, 2001). All of the improvements in hormone levels seen in this study bode well for men and prostate health.

Infertility

A double blind, randomized trial of 30 men suffered from infertility showed that astaxanthin increased the sperm linear velocity and decreased reactive oxygen species and Inhibin B (Comhaire *et al*., 2005) Thus, astaxanthin may benefit users at risk of certain types of infertility.

Ulceration

Astaxanthin may benefit users from certain types of ulcers. Researcher supplemented rats suffered from naproxen-induced gastric antral ulceration with astaxanthin. The oral administration of astaxanthin (dosage 1, 5, and 25 mg/kg of body weight) showed a significant protection against naproxen (80 mg/kg of body weight)-induced gastric antral ulcer and inhibited elevation of the lipid peroxide level in gastric mucosa. It was also found that pretreatment of astaxanthin resulted in a significant increase in the activities of radical scavenging enzymes such as superoxide dismutase, catalase, and glutathione peroxidase. The acute gastric mucosal lesion induced by naproxen nearly disappeared after the pretreatment of astaxanthin (Kim *et al*., 2005)

Conclusions and future of astaxanthin

Numerous scientific papers and research indicate that natural Astaxanthin has great potential as a superb antioxidant with beneficial effects on various human diseases and physiological phenomena. Further studies will strengthen the scientific basis for the role of natural Astaxanthin as a unique and efficient antioxidant and for its use in different commercial purposes including health products. It is expected that in a few years' time, the natural Astaxanthin market will significantly rise and

new line of applications will be designed for the treatment of specific diseases and other uses. Some of these new products will contain other components as well the cocktail concept, such as other carotenoids, antioxidants, vitamins, polyunsaturated fatty acids, minerals, and more. Because of its immense beneficial properties this commercialization will become multi-faceted, to include products for the food, feed, coloring agent, dyes and paints, cosmetics, pharmaceutical and Nutraceutical industries.

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