



International Journal of Preclinical & Pharmaceutical Research

Journal homepage: www.preclinicaljournal.com

ASTASHINE CAPSULES: AN EXCELLENT CHOICE FOR A HEALTHY LIFESTYLE

**Govind Shukla, Jyothika Vanamali, Nagalakshmi Yaparthy, G.Santosh Kumar,
C.J. Sampath Kumar**

Lactonova Nutripharm (P) Ltd, Makers of ASTASHINE capsules, 81/3, IDA Mallapur, Hyderabad, Telangana, India-500 076.

ABSTRACT

ASTASHINE capsule contains natural astaxanthin from *Haematococcus pluvialis*. In ASTASHINE capsules, a xanthophyll carotenoid, is a nutrient with unique cell membrane actions and diverse clinical benefits. This molecule neutralizes free radicals or other oxidants by either accepting or donating electrons, and without being destroyed or becoming a pro-oxidant in the process. Its linear, polar-nonpolar-polar molecular layout equips it to precisely insert into the membrane and span its entire width. In this position, astaxanthin can intercept reactive molecular species within the membrane's hydrophobic interior and along its hydrophilic boundaries. Clinically, astaxanthin has shown diverse benefits, with excellent safety and tolerability. The present Article reviews the role of ASTASHINE capsules as mother's nature most powerful Antioxidant.

Key Words: Astashine capsule, Natural Astaxanthin, Antioxidant,

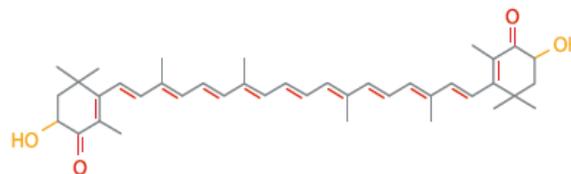
INTRODUCTION

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 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 differs in the configuration of the two hydroxyl groups on the molecule. The 3S, 30S 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].



Corresponding Author

Govind shukla

Email: Email:- govindbbd@gmail.com

Astaxanthin is

500 times stronger than Vitamin E

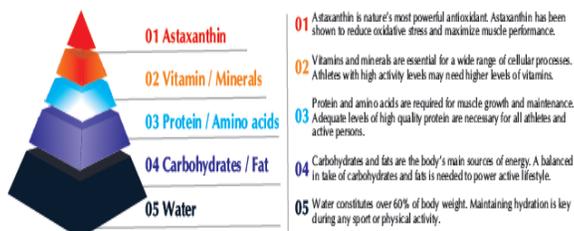
560 times stronger than Green tea catechins

800 times stronger than CoQ 10

3000 times stronger than Resveratrol

6000 times stronger than Vitamin C

Nishida Y, et al (2007). Carotenoid Science, 11, 16-20.



Composition:

Astaxanthin (Astareal) - 2mg (Naturally derived from *Haematococcus pulvalialis* algae extract, which is microencapsulated)

PHARMACOLOGY

NEUROVASCULAR PROTECTION: Decrease the oxidation of Red blood cells, decreases the incidence of ischemic stroke, and improves memory and learning.

SKIN AGING DEFENCE: Prevents UV induces wrinkle formation, skin sagging, and age spots; improves skin elasticity and skin dryness.

LIVER HEALTH and METABOLIC SYNDROME: Inhibits progression of fatty liver disease, increases fat burning, and decreases inflammatory markers.

LOWERNING GASTRIC INFLAMMATION: Reduces *Helicobacter pylori* inflammation, gastric ulceration, indigestion, acid reflux, heart burn and stomach pain.

MUSCLE RESILIENCE: Enhances power output, endurance, and recovery after exercise; prevents muscle damage and muscle atrophy.

EYE FATIGUE RELIEVE: Reduces eye fatigue in subjects suffering from visual display syndrome.

IMMUNE SYSTEM BOOSTER: Reduces DNA damage in immune cells and enhances the immune response.

CARDIOVASCULAR HEALTH: Fights atherosclerosis by decreasing blood pressure, lipid deposits, lipid peroxidation and vascular inflammation.

ANTI-DIABETES: improves pancreatic function, insulin resistance, and insulin sensitivity.

KIDNEY PROTECTION: Reduces glucose toxicity and kidney inflammation.

FERTILITY: Improves sperm parameters and fertility.

CAPILLARY CIRCULATION: improves blood flow and capillary integrity; reduces blood cell oxidation and the risk of thrombosis.

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 b-carotene, a-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 peroxy 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.

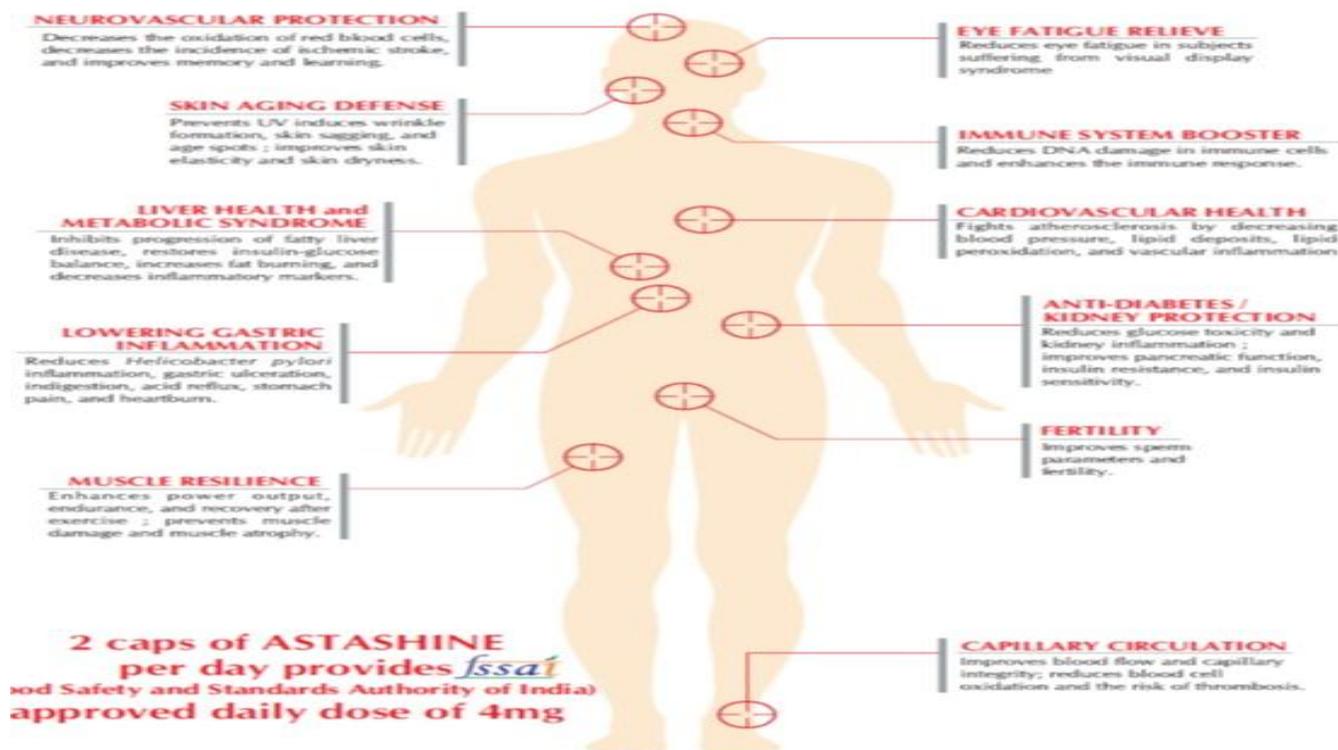
Oxidative damage has been linked to aging, atherogenesis, ischemia-reperfusion injury, infant retinopathy, age-related macular degeneration and carcinogenesis [7].

Dietary antioxidants, such as carotenoids, might help to prevent and fight several human diseases. Carotenoids are 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 b-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 *Helicobacter pylori* infection, aging and age-related diseases, or the promotion of the immune response, liver function and heart, eye, joint and prostate health.

Astaxanthin is extensively researched in peer reviewed in clinical studies

Effect of Astaxanthin on individual organs

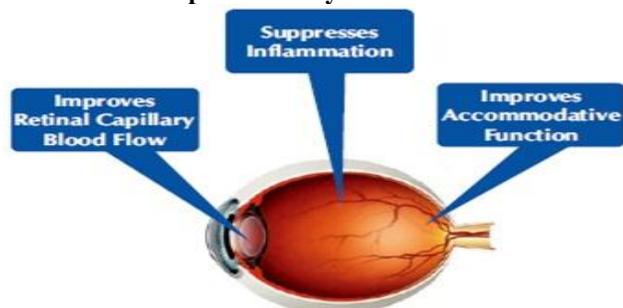


ASTASHINE capsules as a photoprotectant

Exposure of lipids and tissues to light, especially UV-light, can lead to production of singlet oxygen and free radicals and photo-oxidative damage of these lipids and tissues [7].

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

ASTASHINE capsules and eye health

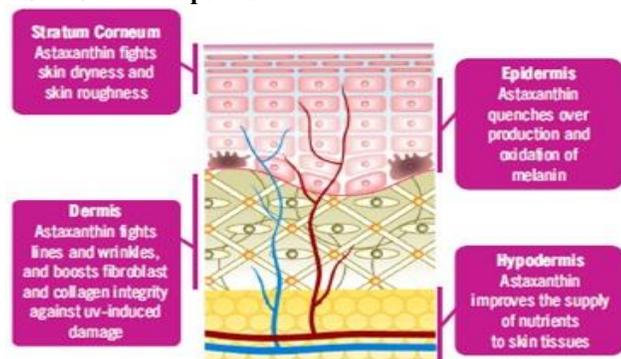


Two of the leading causes of visual impairment and blindness are age-related macular degeneration (AMD) and age-related cataracts. Both diseases appear to be related to light-induced oxidative processes within the eye [7,15]. It is therefore not surprising that factors related to oxidation have been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

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

light and oxidation of retinal tissues pointing to the potential of astaxanthin for eyehealth maintenance.

ASTASHINE capsules and skin health



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

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

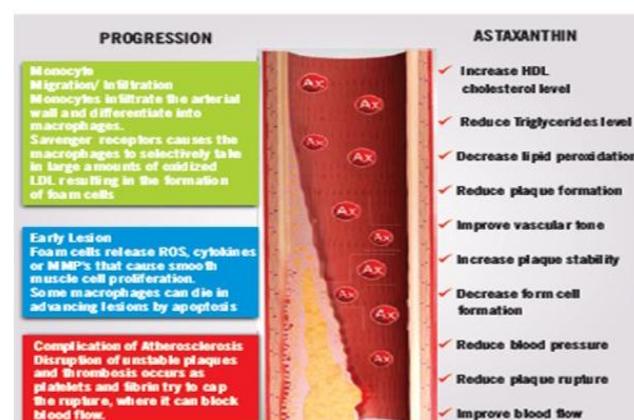
ASTASHINE capsules and inflammation

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

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

ASTASHINE capsules and heart health

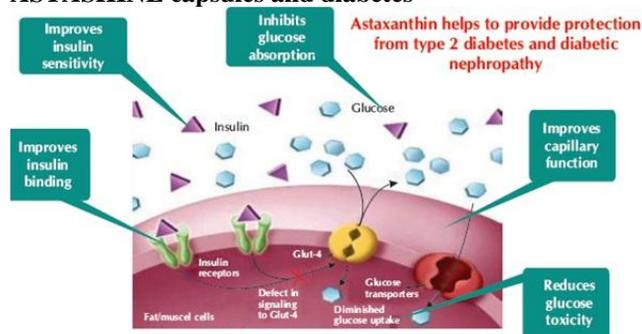
Potential Benefits of Astaxanthin for Atherosclerosis



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

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

ASTASHINE capsules and diabetes



ASTASHINE capsules and cellular health

In the mitochondria, multiple oxidative chain reactions generate the energy needed by the cell but produce large amounts of free radicals that need to be neutralized to maintain proper mitochondrial 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 liver cells can be as high as 100 times that of vitamin E [12].

This highlights the unique capacity of astaxanthin in helping to preserve 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 junction communications might explain some of the anti-cancer activities of astaxanthin.

Anti-cancer properties of ASTASHINE capsules

Several studies have demonstrated the anti-cancer activity of astaxanthin in mammals. Astaxanthin protected 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 *b*-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 *b*-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]. 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 ASTASHINE capsules 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.

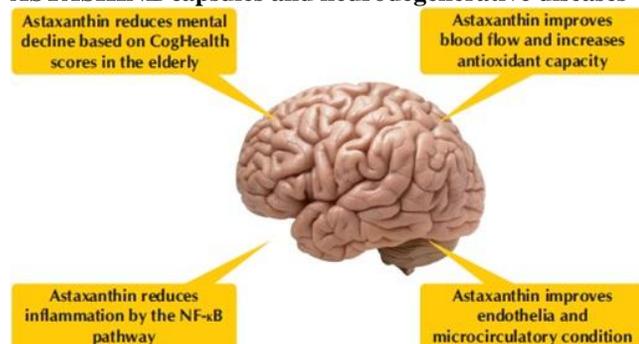
Astaxanthin is much more effective than vitamin E at protecting mitochondria from rat liver cells against lipid peroxidation [12]. Astaxanthin also induces xenobiotic-metabolizing enzymes in rat liver, a process that could help prevent carcinogenesis [52]. Astaxanthin can induce xenobiotic-metabolizing enzymes in the lung and kidney [50].

ASTASHINE capsules 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].

ASTASHINE capsules 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]. Astaxanthin can cross the blood brain barrier in mammals and can extend its antioxidant benefits beyond that barrier.

Usage: As a food supplement combination of antioxidants to improve health and vitality.

Contra-indications: Product is contra-indicated in persons with Known hypersensitivity to any component of the product hypersensitivity to any component of the product.

Recommended usage : Adults: two capsules per day along with food.

“Do not exceed the recommended daily dose”

“Food supplements must not be used as a substitute for a varied and balanced diet and a healthy lifestyle”

“This product is not intended to diagnose, treat, cure or prevent any disease(s)”

Administration: Taken by oral route at anytime with food.

Precautions:

Food Supplements must not be used as a substitute for a varied and balanced diet and a healthy lifestyle.

This Product is not intended to diagnose, treat, cure or prevent any diseases.

Do not exceed the recommended daily dose.

Warnings: If you are taking any prescribed medication or

has any medical conditions or under age group 17 year always consults doctor or healthcare practitioner before taking supplements.

Side Effects: No significant side effects have yet been reported.

Storage: store in a cool, dry and dark place. Keep out of reach of children

Safety/Toxicity

Astaxanthin has demonstrated safety in numerous human clinical trials. In one open-label clinical study on subjects with metabolic syndrome (n=17), [63]. Astaxanthin (16 mg/day, for three months) significantly raised blood bilirubin ($p \leq 0.05$), potassium ($p \leq 0.05$), and creatine kinase ($p \leq 0.01$), although all three values remained within normal range. Also, astaxanthin significantly lowered the liver enzyme gamma-glutamyl transpeptidase (GGTP; $p \leq 0.05$). Since the researchers noted this enzyme was abnormally elevated in 11 of the 17 subjects at baseline, this astaxanthin effect may have been beneficial.

Animal experiments have investigated astaxanthin at levels well over 120 mg/day in human equivalents, without causing apparent harm. Hoffman-La Roche confirmed its safety with extensive tests, including acute toxicity, mutagenicity, teratogenicity, embryotoxicity, and reproductive toxicity.

Suggested Dosage

The doses of astaxanthin used in clinical trials have ranged from 1 mg/day to 40 mg/day (with the majority in the 6-12 mg range); single-dose pharmacokinetic studies used up to 100 mg per dose. As a dietary supplement, astaxanthin should be taken along with fats, with or immediately prior to meals, to ensure its optimal absorption. [64].

Conclusion

Astaxanthin, a xanthophyll carotenoid, is a nutrient with unique cell membrane actions and diverse clinical benefits. This molecule neutralizes free radicals or other oxidants by either accepting or donating electrons, and without being destroyed or becoming a pro-oxidant in the process. Its linear, polar-nonpolar-polar molecular layout equips it to precisely insert into the membrane and span its entire width. In this position, astaxanthin can intercept reactive molecular species within the membrane's hydrophobic interior and along its hydrophilic boundaries. Clinically, astaxanthin has shown diverse benefits, with excellent safety and tolerability. In double-blind, randomized controlled trials (RCTs), astaxanthin lowered oxidative stress in overweight and obese subjects and in smokers. It blocked oxidative DNA damage, lowered C-reactive protein (CRP) and other inflammation biomarkers, and boosted immunity in the tuberculin skin test. Astaxanthin lowered triglycerides and raised HDL-cholesterol in another trial and improved blood flow in an

experimental microcirculation model. It improved cognition in a small clinical trial and boosted proliferation and differentiation of cultured nerve stem cells. In several Japanese RCTs, astaxanthin improved visual acuity and eye accommodation. It improved reproductive performance in men and reflux symptoms in *H. pylori* patients. In preliminary trials it showed promise for sports performance (soccer). In cultured cells, astaxanthin

protected the mitochondria against endogenous oxygen radicals, conserved their redox (antioxidant) capacity, and enhanced their energy production efficiency. The concentrations used in these cells would be attainable in humans by modest dietary intakes. Astaxanthin's clinical success extends beyond protection against oxidative stress and inflammation, to demonstrable promise for slowing age-related functional decline.

REFERENCES

- Lorenz, R.T. and Cysewski, G.R. Commercial potential for Haematococcus microalgae as a natural source of astaxanthin. *Trends Biotechnol*, 18, 2000, 160–167.
- Olaizola, M. and Huntley, M.E. Recent advances in commercial production of astaxanthin from microalgae. In Biomaterials and Bioprocessing Science Publishers, 2003.
- Turujman, S.A. et al. Rapid liquid chromatographic method to distinguish wild salmon from aqua cultured salmon fed synthetic astaxanthin. *J. AOAC Int*, 80, 1997, 622–632.
- Jyonouchi, H. et al. Effect of carotenoids on in vitro immunoglobulin production by human peripheral blood mononuclear cells: astaxanthin, a carotenoid without vitamin A activity, enhances in vitro immunoglobulin production in response to a T-dependent stimulant and antigen. *Nutr. Cancer*, 23, 1995, 171–183.
- Furr, H.C. and Clark, R.M. Intestinal absorption and tissue distribution of carotenoids. *J. Nutr. Biochem*, 1997, 8, 364–377.
- Sterlie, M. et al. Plasma appearance and distribution of astaxanthin E/Z isomers in plasma lipoproteins of after single dose administration of astaxanthin. *J. Nutr. Biochem*, 11, 2000, 482–490.
- Papas, A.M. Antioxidant Status, Diet, Nutrition, and Health. CRC Press, 1999.
- Mortensen, A. et al. Comparative mechanisms and rates of free radical scavenging by carotenoid antioxidants. *FEBS Lett*, 418, 1997, 91–97.
- Beutner, S. et al. Quantitative assessment of antioxidant properties of natural colorants and phytochemicals: carotenoids, flavonoids, phenols and indigoids. The role of β -carotene in antioxidant functions. *J. Sci. Food Agric*, 81, 2001, 559–568.
- Palozza, P. and Krinsky, N.I. Astaxanthin and canthaxanthin are potent antioxidants in a membrane model. *Arch. Biochem and Biophys*, 297, 1992, 291–295.
- Naguib, Y.M.A. Antioxidant activities of astaxanthin and related carotenoids. *J. Agric. Food Chem*, 48, 2000, 1150–1154.
- Kurashige, M. et al. Inhibition of oxidative injury of biological membranes by astaxanthin. *Physiol. Chem. Phys. Med. NMR*, 22, 1990, 27–38.
- Shimidzu, N. et al. Carotenoids as singlet oxygen quenchers in marine organisms. *Fish. Sci*, 62, 1996, 134–137.
- O'Connor, I. and O'Brien, N. Modulation of UVA light-induced oxidative stress by beta-carotene, lutein and astaxanthin in cultured fibroblasts. *J. Dermatol. Sci*, 16, 1998, 226–230.
- Jacques, P. The potential preventive effects of vitamins for cataract and age-related macular degeneration. *Int. J. Vitam. Nutr. Res*, 69, 1999, 198–205.
- Lyle, B.J. et al. Antioxidant intake and risk of incident age related nuclear cataracts in the Beaver Dam Eye Study. *Am. J. Epidemiol*, 149, 1999, 801–809.
- Seddon, J.M. et al. Dietary carotenoids, vitamins A, C, and E, and advanced age-related macular degeneration. *J. Am. Med. Assoc*, 272, 1994, 1413–1420.
- Landrum, J.T. et al. Analysis of zeaxanthin distribution within individual human retinas. *Methods Enzymol*, 299, 1999, 457–467.
- Tso, M.O.M. and Lam, T-T. Method of Retarding and Ameliorating Central Nervous System and Eye Damage. U.S. Patent #5527533, 1996.
- Fuchs, J. Potentials and limitations of the natural antioxidants RRR-alpha-tocopherol, L-ascorbic acid and beta-carotene in cutaneous photo protection. *Free Radic. Biol. Med*, 25, 1998, 848–873.
- Lee, J. et al. Carotenoid supplementation reduces erythema in human skin after simulated solar radiation exposure. *Proc. Soc. Exp. Biol. Med*, 223, 2000, 170–174.
- Stahl, W. et al. Carotenoids and carotenoids plus vitamin E protect against ultraviolet light-induced erythema in humans. *Am. J. Clin. Nutr*, 71, 2000, 795–798.
- Meyers, S.P. The biological role of astaxanthin in salmonids and other aquatic species. First International Symposium on Nat. Colors for Foods, Nutraceuticals, Beverages and Confectionary, Amherst, USA, 1993.
- Torissen, O.J. et al. Pigmentation of salmonids – carotenoid deposition and metabolism. *CRC Crit. Rev. Aquat. Sci*, 1, 1989, 209–225.

25. Savoure, N. et al. Vitamin A status and metabolism of cutaneous polyamines in the hairless mouse after UV irradiation: action of b-carotene and astaxanthin. *Int. J. Vitam. Nutr. Res*, 65, 1995, 79–86.
26. Black, H. Radical interception by carotenoids and effects on UV carcinogenesis. *Nutr. Cancer*, 31, 1998, 212–217.
27. Aghdassi, E, Allard, J.P. Breath alkanes as a marker of oxidative stress in different clinical conditions. *Free Radic. Biol. Med*, 28, 2000, 880–886.
28. Aw, T.Y. Molecular and cellular responses to oxidative stress and changes in oxidation-reduction imbalance in the intestine. *Am. J. Clin. Nutr*, 70, 1999, 557–565.
29. Greene, L. Asthma and oxidant stress: nutritional, environmental, and genetic risk factors. *J. Am. Coll. Nutr*, 14, 1995, 317–324.
30. Dekkers, J. et al. The role of antioxidant vitamins and enzymes in the prevention of exercise-induced muscle damage. *Sports Med*, 21, 1996, 213–238.
31. Bennedsen, M. et al. Treatment of H. pylori infected mice with antioxidant astaxanthin reduces gastric inflammation, bacterial load and modulates cytokine release by splenocytes. *Immunol. Lett*, 70, 1999, 185–189.
32. Frei, B. Cardiovascular disease and nutrient antioxidants: role of low-density lipoprotein oxidation. *Crit. Rev. Food Sci. Nutr*, 35, 1995, 83–98.
33. Kritchevsky, S.B. β -Carotene, carotenoids and the prevention of coronary heart disease. *J. Nutr*, 129, 1999, 5–8.
34. Miki, W. et al. Astaxanthin-Containing Drink. Japanese, Patent #10155459, 1998.
35. Murillo, E. Effect of hypercolesterolemico de la cantaxantina y la astaxantina en ratas. *Arch. Latinoam. Nutr*, 42, 1992, 409–413.
36. Tracy, R.P. Inflammation markers and coronary heart disease. *Curr. Opin. Lipidol*, 10, 1999, 435–441.
37. Gershon, D. The mitochondrial theory of aging: Is the culprit a faulty disposal system rather than indigenous mitochondrial alterations? *Exp. Gerontol*, 34, 1999, 613–619.
38. Goto, S. et al. Efficient radical trapping at the surface and inside the phospholipid membrane is responsible for highly potent antiperoxidative activity of the carotenoid astaxanthin. *Biochem. Biophys. Acta*, 1512, 2001, 251–258.
39. Barros, M.P. et al. Astaxanthin and peridinin inhibit oxidative damage in Fe²⁺, β -loaded liposomes: Scavenging oxy radicals or changing membrane permeability? *Biochem. Biophys. Res. Commun*, 288, 2001, 225–232.
40. Matsushita, Y. et al. Antioxidant activity of polar carotenoids including astaxanthin- β -glucoside from marine bacterium on PC liposomes. *Fish. Sci*, 66, 2000, 980–985.
41. Allen, R.G. and Tresini, M. Oxidative stress and gene regulation. *Free Radic. Biol. Med*, 28, 2000, 463–499.
42. Bertram, J.S. Carotenoids and gene regulation. *Nutr. Rev*, 57, 1999, 182–191.
43. Kistler, A. et al. Metabolism and CYP-inducer properties of astaxanthin in man and primary human hepatocytes. *Arch. Toxicol*, 75, 2002, 665–675.
44. Tanaka, T. et al. Chemoprevention of mouse urinary bladder carcinogenesis by the naturally occurring carotenoid astaxanthin. *Carcinogenesis*, 15, 1994, 15–19.
45. Tanaka, T. et al. Chemoprevention of rat oral carcinogenesis by naturally occurring xanthophylls, astaxanthin and canthaxanthin. *Cancer Res*, 55, 1995, 4059–4064.
46. Tanaka, T. et al. Suppression of azomethane-induced rat colon carcinogenesis by dietary administration of naturally occurring xanthophylls astaxanthin and canthaxanthin during the post initiation phase. *Carcinogenesis*, 16, 1995, 2957–2963.
47. Chew, B.P. et al. A comparison of the anticancer activities of dietary b-carotene, canthaxanthin and astaxanthin in mice in vivo. *Anticancer Res*, 19, 1999, 1849–1854.
48. Anderson, M. Method of Inhibiting 5-a Reductase with Astaxanthin to Prevent and Treat Benign Prostate Hyperplasia (BPH) and Prostate Cancer in Human Males. US Patent #6277417, 2001.
49. Kurihara, H. et al. Contribution of the antioxidative property of astaxanthin to its protective effect on the promotion of cancer metastasis in mice treated with restraint stress. *Life Sci*, 70, 2002, 2509–2520.
50. Jewell, C. and O'Brien, N. Effect of dietary supplementation with carotenoids on xenobiotic metabolizing enzymes in the liver, lung, kidney and small intestine of the rat. *Br. J. Nutr*, 81, 1999, 235–242.
51. Jyonouchi, H. et al. Antitumor activity of astaxanthin and its mode of action. *Nutr. Cancer*, 36, 2000, 59–65.
52. Gradelet, S. et al. Dietary carotenoids inhibit aflatoxin B1-induced liver preneoplastic foci and DNA damage in the rat: role of the modulation of aflatoxin, B1 metabolism. *Carcinogenesis*, 19, 1998, 403–411.
53. Hughes, D.A. Effects of dietary antioxidants on the immune function of middle-aged adults. *Proc. Nutr. Soc*, 58, 1999, 79–84.
54. Jyonouchi, H. et al. Studies of immunomodulating actions of carotenoids. II. Astaxanthin enhances in vitro antibody production to T-dependent antigens without facilitating polyclonal B-cell activation. *Nutr. Cancer*, 19, 1993, 269–280.
55. Jyonouchi, H. et al. Immunomodulating actions of carotenoids: enhancement of in vivo and in vitro antibody production to T-dependent antigens. *Nutr. Cancer*, 21, 1994, 47–58.

56. Okai, Y. and Higashi-Okai, K. Possible immunomodulating activities of carotenoids in, in vitro cell culture experiments. *Int. J. Immuno pharmacol*, 18, 1996, 753–758.
57. Jyonouchi, H. et al. Astaxanthin, a carotenoid without vitamin A activity, augments antibody responses in cultures including T-helper cell clones and suboptimal doses of antigen. *J. Nutr*, 124, 1995, 2483–2492.
58. Facchinetti, F. et al. Free radicals as mediators of neuronal injury. *Cell. Mol. Neurobiol*, 18, 1998, 667–682.
59. Grant, W.B. Dietary links to Alzheimer's disease. *J. Alzheimers Dis*, 2, 1997, 42–55.
60. Borlongan, C. et al. Free radical damage and oxidative stress in Huntington's disease. *J. Fla. Med. Assoc*, 83, 1996, 335–341.
61. De Rijk, M. et al. Dietary antioxidants and Parkinson disease. The Rotterdam Study. *Arch. Neurol*, 54, 1997, 762–765.
62. Ferrante, R. et al. Evidence of increased oxidative damage in both sporadic and familial amyotrophic lateral sclerosis. *J. Neurochem*, 69, 1997, 2064–2074.
63. Uchiyama A, Okada Y. Clinical efficacy of astaxanthin-containing *Haematococcus pluvialis* extract for the volunteers at risk of metabolic syndrome. *J Clin Biochem Nutr*, 43, 2008, 390-393.
64. Osterlie M, Bjerkeng B, Liaaen-Jensen S. Plasma appearance and distribution of astaxanthin E/Z and R/S isomers in plasma lipoproteins of men after single dose administration of astaxanthin. *J Nutr Biochem*, 11, 2000, 482-490.