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A robust clinical information on king of carotenoids: a systematic review of the literature

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Abstract

Astaxanthin is a red carotenoid pigment extensively found in living organisms. Though Astaxanthin is a carotenoid compound, unlike β-carotene (a vitamin A precursor), cannot be converted to vitamin A. Astaxanthin, a potent antioxidant,with other biological effects protects cell membranes from harmful damage in the body. Studies suggest Astaxanthin may be effective in treating diseases, including cardiovascular, immune disorders, tumor, diabetes, neurodegenerative conditions and inflammatory conditions. Recent studies on Astaxanthin have shown enhancing immune response and decreasing DNA damage in humans. Astaxanthin is capable of crossing the blood-brain barrier in mammals.

Keywords: Astaxanthin, Antioxidant, Immune response

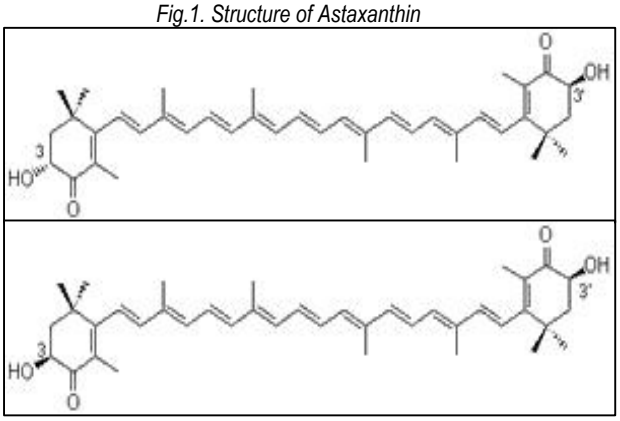
Introduction

Astaxanthin (xanthophylls group of carotenoids or oxygenated carotenoids) is a naturally occurring, rich in ketocarotenoids with an anti-oxidant effect. The –OH and =O functional group present in ending ionone ring is responsible for powerful anti-oxidant activity (Ikeuchi *et al.,* 2006). The comparison of Astaxanthin and β-carotenoids molecule more or less similar, except small difference in that the end of the molecule present in –OH and =O groups in Astaxanthin which results in varied functional abilities. The chemical difference between natural and synthetic Astaxanthin is evidenced in sterochemical orientation of the molecule (Iwasaki *et al.,* 2006).

Astaxanthin exist three main enantiomeric forms, termed 3S-3S', 3R-3S' depending upon spectral arrangement of –OH groups. A recent study showed that salmon is an Astaxanthin isomer. The pigment in salmon found is 3S-3S', enantiomer forms, identical to that found in Haematococcus synthetic. Petrochemical sources contain a mixture of all enantiomers of Astaxanthin. The chemical synthesis of Astaxanthin is 3S-3S' enantiomers (meso form). The stereoisomer found in Haemotococcus is 3S-3'S. While Astaxanthin in algae and fish present as mono and di ester of fatty acid, the synthetic Astaxanthin is a free hydroxyl. In nutraceutical application natural Astaxanthin ester is more stable than unoxidised free hydroxyl has a longer shelf life

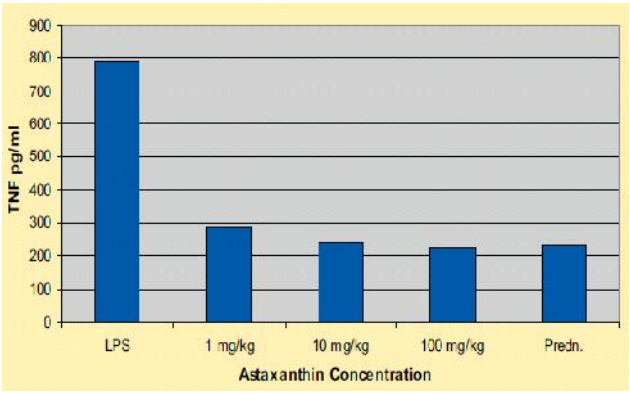
(Naguib, 2000). The structure Astaxanthin was presented in the Fig.1.

Fig.1. Structure of Astaxanthin



Astaxanthin works to suppress different inflammatory mediators. Among these mediators is tumour necrosis factor alpha (TNF-a), prostaglandin E-2(PGE-2), interleukin 1B (1L-1b) and nitric oxide (NO). In one experiment done with mice and also in-vitro, Astaxanthin was shown to suppress TNF-a, PGE-2, 1L-1b, NO as well as the Cox-2 enzyme and nuclear factor kappa-B. Astaxanthin was shown in vitro to decrease the production of

Fig.2.Astaxanthin suppresses production of tumor necrosis factor-alpha (TNF- α)



NO, PGE-2 and TNF-A. This study also considered Astaxanthin for its anti-inflammatory effect on rats eyes.

Astaxanthin had a "dose dependent ocular anti-inflammatory effect, through directly blocking nitric oxide synthase enzyme activity suppressing NO, PGE-2 and TNF-a production". Basically,this study proved that Astaxanthin reduces inflammation of the eye, cause of many different ailments (Takahashi *et al.,* 2005). Fig.2-5 depicts how Astaxanthin works through multiple pathways to combat

Fig.3.Astaxanthin suppresses production of prostaglandin (PGE2)

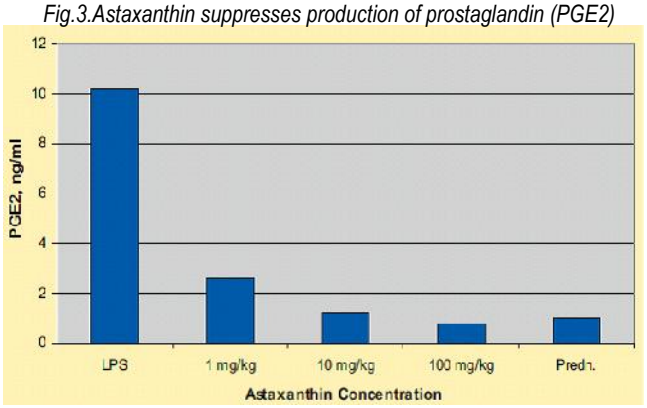


Fig.4. Astaxanthin suppresses production of Nitric Oxide (NO)

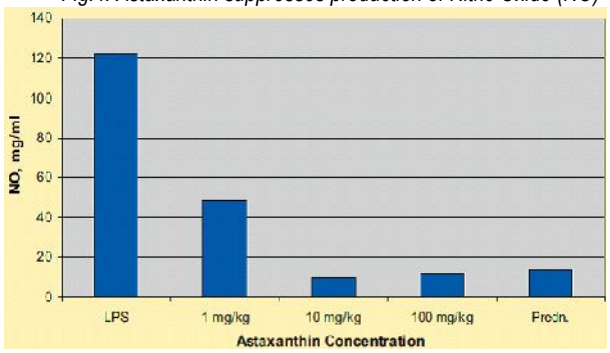
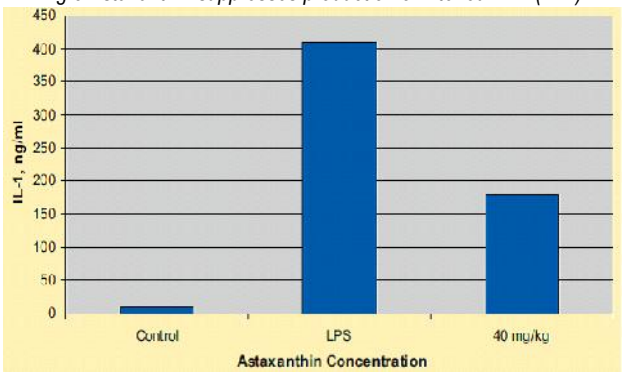


Fig.5.Astaxanthin suppresses production of interleukin-1 (IL-1)

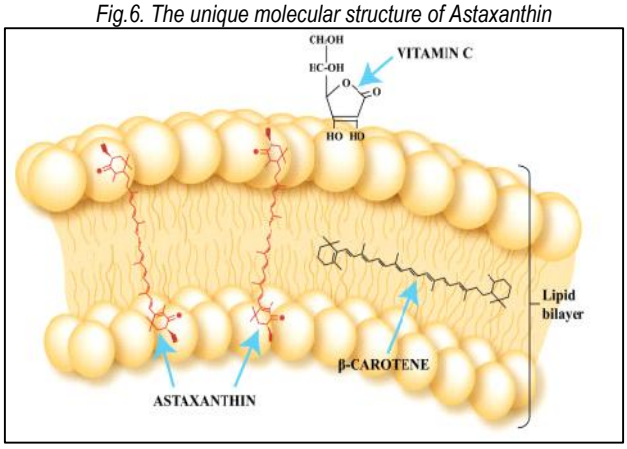


inflammation.

Astaxanthin pathway combats inflammation through inhibition of the cyclooxygenase enzymes (Cox-1 and Cox-2). The laboratory found that Celecoxib (4.4 times stronger) was more than 300 times stronger in Cox-2 inhibition than natural Astaxanthin. However, in Cox-1 inhibition, the two were almost of the same strength. The ratio of Cox-2 to Cox-1 inhibition showed differences for each product. For Celecoxib the ratio was 78.5, while for natural Astaxanthin it was only 1.1. This indicates that COX-1 and COX-2 inhibition by natural Astaxanthin is almost same.Fig.6.

shows the unique molecular structure of Astaxanthin. Astaxanthin's unique molecular structure enables it to pass through the cell membrane which giving a superior protection to the cell membrane though B-carotene and vitamin C can only be similarly positioned justaposed with lipid layer (Suzuki *et al.,* 2006).

Fig.6. The unique molecular structure of Astaxanthin



Natural Astaxanthin efficient uptake accumulates within the organs and in cells. As a very effective and fat soluble antioxidant, Astaxanthin protects lipids and membranes in the cell from oxidation. Thereby Astaxanthin supports the functionality and vitality by protecting the cell membranes from damage, Astaxanthin also possess strong anti-inflammatory effects. (Terao,1989).

Under certain conditions, the anti-oxidant property becomes pro-oxidant and causes negative effects by oxidation of the body, examples of this property are β-carotene, Lycopene and Zeaxanthin. Some antioxidants vitamin-C, vitamin-E and zinc can also became pro-oxidants. This is an another important factor as Astaxanthin an anti-oxidant, never becomes a pro-oxidant, proving it is a far superior anti-oxidant compared to others (Yoshida *et al.,* 2009).

Anti-inflammatory effect

By decreasing inflammation Astaxanthin can help prevent and treatment a number of problems that result directly from inflammation including rheumatoid arthritis and other common repetitive stress injuries like carpal tunnel syndrome and tennis elbow (Fassett , 2009).

Measuring of the silent inflammation can be established in two ways.

1. Blood test: Measuring C-reactive protein (CRP). In one study, natural Astaxanthin was found to reduce CRP levels by 20% in just eight weeks. Another study found Astaxanthin caused 43% of people with high CRP levels to drop into the average range.This CRP is a better predictor of risk, than lipids, of impending heart attack. CRP is produced in liver and coronary arteries, during inflammatory processes and released into bloodstream.
2. Sedimentation rate: Erythrocyte sedimentation rate (ESR) which is especially helpfully in monitoring rheumatoid arthritis and other autoimmune diseases.

Astaxanthin suppresses a variety of inflammatory mediators-including tumor necrosis factor alpha, a major prostaglandin and a major interleukin, nitric oxide, COX-1 and COX-2 enzymes. It produces effects than NSAIDs but it does not result in the dangerous side effects (Ohgami *et al.,* 2003).

CVS

Cholesterol is a primary indicator of cardiovascular health. It is now established that the gauge of health comes not so much from total cholesterol levels as from the ratio of high-density lipoproteins (HDL) or (good cholesterol) to low-density lipoproteins (LDL) or (bad cholesterol). The study of cholesterol levels of rat fed diets containing 1000 parts per million bete-carotene, canthaxanthin and Astaxanthin for 30days. In this Astaxanthin and canthaxanthin showed significant increases in HDL. Astaxanthin can help improve blood lipid profile by decreasing low density lipoprotein (LDL), triglycerides and increasing high density lipoprotein (HDL). This has been demonstrated in both human and animal trials. An early study in rats demonstrated that Astaxanthin raised HDL, the good cholesterol (Tso *et al.,* 1996).

A later study tested both Astaxanthin and Vitamin E in rabbits that had high cholesterol. This study found that the both supplements, particularly Astaxanthin improved plaque stability in the arteries compared to rabbits ingesting Vitamin E and in the control group. A third animal study was done recently on rats, showed that Astaxanthin increased HDL while decreasing both triglycerides and nonestrified fatty acids in the blood (Jyonouchi *et al.,* 2000).

In human trials invitro and invivo found it affected the LDL levels. The in-vitro test showed that Astaxanthin dose-dependently prolonged the oxidation lag time of LDL. The test was in humans doses at low 1.8mg per day and high as 21.6mg per day for 14 days. This study found that all four doses positively affected LDL oxidation lag-at 1.8mg per day it was 5% longer; at 3.6 mg it was 26% longer; at 14.4 mg it was 42% longer; and at the highest dose of 21.6 mg the upward trend stopped and the lag time wa only 31% longer. This suggests that the optimum dose for blood lipid profiles is significantly less than 21.6 mg per day. This study concluded that that consumption of Astaxanthin inhibits LDL oxidation and possibly therefore contributes to the prevention of atherosclerosis (Ikeuchi *et al.,* 2006).

Dementia

Orally administered Astaxanthin was associated with significant reductions compound called phospholipid hydroperoxides [PLOOH], which accumulates abnormally in RBC [erythrocytes]. On the basis of these points, Astaxanthin has potential to act as an important antioxidant in erythrocytes and preventing Dementia (Fassett *et al.,* 2009).

Eye

Some carotenoids have shown to help protect the retina of the eye from oxidative damage. The lens of the eye focuses light onto the photo sensitive retina, which transmit signal to the brain. The central area of the retina – the macula, having high density photo receptors to provide visual acuity. Oxidation from sunlight exposure degrades membranes and leads to damage or destruction of photo receptor cells (Tso *et al.,* 1996).

A recent rat study indicates, Astaxanthin is able to cross the blood retinal barrier and anti-Oxidant effect to ameliorate retina injury by light induced oxidation and protecting photo receptors from degradation. The carotenoid pigments lutein and Zeaxanthin which concentrate in the macula, absorb blue light and singlet oxygen radicals. The Astaxanthin has also excellent singlet oxygen radicals (Nagaki *et al.,* 2006). The photo receptor cells are outer neuronal layer of the retina which is a component of the central nervous system. The study results such as Astaxanthin may prevent and treat neuronal damage associated with age related macular degradation and may also be useful in the treatment of ischemic reperfusion injuries (Jyonouchi *et al.,* 2000).

Prevent the gastric damage

The first study, the non steroidal anti inflammatory naproxen was given to rats. It causes ulcerative lesions in the stomach. Rats fed Astaxanthin at 3 different dosage level provided significant protection against naproxen's deleterious effects on the stomach lining. Also pretreatment with astaxanthin increased the activity of free radical scavenging enzyme super oxide dismutase (SOD), catalase and glutothionone peroxidase. Astaxanthin removes the lipid peroxidase and free radicals induced by naproxen thus inhibiting gastric ulceration.

The second study involved in ethyl alcohol, the active ingredients in whisky, rum, vodka, causes ulcerative gastric lesions in humans, when consumed in excess. In rats, causes ulcerative lesions in the stomach. Rats fed Astaxanthin at 3 different dosage level had significant protection against ethyl alcohol deleterious effects on the stomach lining. Also pre-treatment with astaxanthin increased the activity of free radical scavenging enzyme super oxide dismutase (SOD), catalase and glutothionone peroxidase, resulting in removal of lipid peroxidase and free radicals induced by ethyl alcohol minimising gastric ulceration.

Astaxanthin effect on naproxen, its effects on ethyl alcohol showed significant protection against ulcers, and pre-treatment increased the free radical scavenging activities of SOD, catalase and glutathione peroxidase. "A histologic examination clearly indicated that the acute gastric mucosal lesion induced ethanol nearly disappeared after pre-treatment with Astaxanthin" (Nagaki *et al.,*2005).

Helicobacter pylori, a destructive bacteria found in the stomach in about half of the world population's causes chronic gastritis and stomach ulcers. Left untreated it can lead to stomach cancer and lymphoma. "A lower dietary intake of anti-oxidants such as carotenoids and vitamin C. maybe a contributory factor for the acquisition of *H.pylori* in humans" (Terao,1989).

Diabetics

Astaxanthin may have some benefit in people with diabetes and/or in preventing diabetes. Work on rodent models has been initiated, while we have to wait to prove this benefit in humans. The first study examined a special type of mice that are diabetic and obese, a generally accepted model for type-2 diabetic humans. Astaxanthin significantly reduced the blood glucose level of these mice. "These results indicate that Astaxanthin can exert beneficial effects in diabetes, with preservation of beta-cell function". Diabetes adversely affected many different organs of the body like kidneys causing a condition called "nephropathy".

The second study used the same diabetic, obese mice to examine how Astaxanthin could benefit the kidneys. The results: "After 12 weeks of treatment, the Astaxanthin-treated group showed lower blood glucose level compared with the non-treated group treatment with Astaxanthin retarded the progress and acceleration of diabetic nephropathy in the rodent model of type II diabetes. The result suggested that the antioxidant activity of Astaxanthin reduced the oxidative stress on the kidney and prevents renal cell damage.

The third study that on diabetes was previously cited in the section on cardiovascular benefits. This study in rats showed that after 22 weeks Astaxanthin reduced blood pressure and improved cholesterol and triglycerides profiles, but it also showed reduction of blood glucose levels. Astaxanthin actually decreased the size of fat cells. "These results suggest that Astaxanthin retarded insulin resistance by mechanisms involving the increase of, glucose uptake, level of circulating metabolites and adiponectin.

A recent study in diabetic mice showed that expression levels of genes from the kidneys were decreased by Astaxanthin. This research may lead to a "better understanding of the genes and pathways involved in the anti-diabetic mechanism of Astaxanthin (Shiratori *et al.,* 2005).

Sports nutritive

Astaxanthin was shown to significantly improve sports endurance and performance athletes. Exercise performance improved 55% for those who had taken only 4 mg Astaxanthin daily for six months.

Forty students participated in this double placebo controlled Astaxanthin study. The scientists used algae meal as the Astaxanthin supplement. Twenty students got the real capsule with 4mg Astaxanthin per pill. The other twenty received placebo pills, also for six months. The physical strengths examined were strength/endurance, fitness, and strength by standard exercises. Each student was tested for his or her baseline strengths before the Astaxanthin supplementation started. For the students took real Astaxanthin for six months the average number of squats were 54.9% compared to 27.05% squats in the other group (increased by 19.5%).The increase in the Astaxanthin supplemented group was three times higher than the improvement in the placebo group. None of the other strength tests differed significantly between the groups at the end of the study period. This study concludes that Astaxanthin improves strength and

endurance in sports performance (Aoi *et al.,* 2008).

Obesity

The recent research study demonstrate that mice given Astaxanthin in several different doses, along with high fat diet, had significantly lower body weight and body fat levels compare to mice fed a high fat diet of the same calorie level. Astaxanthin also reduce liver weight, liver and blood triglyceride content and blood cholesterol. Astaxanthin added to high fat, high calorie diet, prevented mice from overweight due to fatty liver and high blood fat levels (Ikeuchi *et al.,* 2006).

The Astaxanthin does not reduce absorption of dietary fat, but instead by increasing the usage of fat as energy source controls the levels. This was supported by a decrease in the respiratory exchange ratio (RER), which indicates that fat was used as fuel, instead of carbohydrates.

In another study the mice are given to Astaxanthin along with daily exercise. They were divided in to four groups. 1. Sedentary, 2. Sedentary + Astaxanthin, 3. Running exercise and 4. Running exercise + Astaxanthin.

After 4 weeks the animals in exercise groups were placed on treadmill to test a range of physical parameters. Similar to the study above the Astaxanthin increased fat usage during exercise and accelerated the normal decrease in body fat that occurs with regular exercise, increasing the movement of fats into the mitochondria for the energy production via enhanced carnitine palmitoyltransferase-I (CPT-I) activity. That Astaxanthin conserved muscle glycogen (a normal fuel source for exercise) and used fat stores instead (Terao , 1989).

Aging

The recent study show that, the Astaxanthin not only protects our skin against the sun when applied topically, it can also provide benefits to ultraviolet (UV) damaged skin, reduced wrinkles and stimulated collagen production. The topical Astaxanthin act as effective skin whitening agent, reducing melanin by 40% and greatly reducing freckles as well as age spots.

The skin was tested before supplementation began to see how much UV light needed to causes erythema(reddening of the skin, sun burn). Then the subjects supplemented with 4 mg of Natural Astaxanthin per day for two weeks. After the two weeks supplementations periods was over, the subjects once again underwent the skin-reddening test. The pre-supplementation and Post-supplementation were then compared. The result was that in only two weeks at a standard dose of just 4 mg per day, there was a statistically significant increase for time necessary for UV radiation to redden the skin. This study proved that Astaxanthin was working as a sunscreen.

Astaxanthin can also help to protect the skin from UV damage when applied topically. A study on hairless mice were separated into three groups: 1) A control group, 2) a group received UVB radiation with plain oil did not contain Astaxanthin in the skin,3) The third group would receive UVB radiation, with Astaxanthin in oil put on their skin. The UVB radiation was continued for 18weeks to stimulate photo-aged skin. The results indicate the Astaxanthin reduced wrinkles when compared to the control-irradiated group. These results suggest that topically applied Astaxanthin, which scavenges singlet oxygen effectively, can play an important role to protect the skin from various photodamages such as lipid peroxidation, sunburn reaction, photo toxicity and photo allergy induced by singlet oxygen (Fassett *et al.,* 2009).

Cosmetics

As stated earlier, the topical Astaxanthin act is an effective skin whitening agent, reducing melanin by 40 precent, and greatly reducing freckles as well as age spots (Nitta *et al*.,2005).

Immune system

Astaxanthin was used in-vitro using samples from the blood of adult (human) volunteers, as well as blood from the umbilical cord.Testing was done with both beta-carotene

and Astaxanthin to increase immune markers in the blood. In this Beta-carotene had no effect while Astaxanthin increased the production of two different forms of immunoglobulin. "This study has shown for the first time Astaxanthin, a carotenoid (without Vitamin A activity) enhance human immunoglobulin production in response to T-dependent stimuli."

One study Astaxanthin was able to change the immune response to *H.pylori*. In another study the Astaxanthin has a positive effects on *H.pylori* and gastro intestinal system. Natural Astaxanthin algae meal inhibited the growth of *H.pylori* in vitro. (Nagaki *et al.,* 2002).

Anti tumour

Astaxanthin in vivo has also inhibited the proliferation of human cancer cell lines. Human colon cancer cell lines were placed in a culture containing Astaxanthin Vs. Asta free. After four days the cell lines in culture containing Astaxanthin were significantly less viable. Astaxanthin also showed inhibitory effects on human prostate cancer cells.

Astaxanthin potential in anti-tumour activity are achieved at feasible blood concentration level, unlike chemotherapy drugs, which are toxic. Astaxanthin ability to enhance immune response in mice has also a corollary effect of exhibiting antitumor activity (Terao ,1989).

Many carcinogens undergo detoxification by xenobiotic-metabolizing enzymes, which divert toxic by-products towards detoxification pathway. Xenobiotic naturally occurring compound and drugs are chemicals that are foreign to the biological system. Xenobiotic metabolism is the physical and chemical changes from uptake to excretion of foreign substance in living organisms (Jyonouchi *et al.,* 2000).

Conclusion

Since our enzymes, muscle function and metabolisms are similar to animal model criticizism is irrelevant. The doses of Astaxanthin used in these animal studies are similar to human doses. The same Astaxanthin doses, at the lowest level of 1.2 mg/kg for mice,translates to a dose of 0.1 grams (100 mg) for humans. At the minimum, humans can take a dose of 0.012 gm. of Astaxanthin from purely dietary sources without any additive dose of Astaxanthin, as study show this dose is effective for reducing blood triglyceride levels, and increasing healthy blood HDL cholesterol level. Further dose have indicated accumulation of drug, since it is fat soluble, so lower doses will be sufficient when subjecting longer durations of supplementations.

Astaxanthin in low doses is efficient than other products in that it has an effect on many different mediators. This is how Astaxanthin can be an effective anti-inflammatory without any negative side effects. Astaxanthin, most powerful natural antioxidant has closely related anti-inflammatory properties, which is a desirable advantage over other antioxidants.

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