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REVIEW ARTICLE

ASTAXANTHIN AND ITS HEALTH EFFECTS

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ABSTRACT

Astaxanthin found in salmon, shrimp, lobster, crayfish and krill belongs to the family of xantophil of carotenoids. Astaxanthin is produced from many microorganisms such as microalg Haematococcus pluvialis and red yeast Phaffa rhodzyma. Astaxanthin is also used for coloring agent in fish feed. Apart from coloring agent astaxanthin has many positive effects on health. Astaxanthin has been shown to be 100 times stronger than vitamin E against lipid peroxidation and 40 times effective than β carotene on scavenging singlet oxygen. It has been demonstrated that astaxanthin has protective and therapeutic effects on mainly including oxidative stress, many cancer types, diabetes mellitus, cardiovasculer diseases. In this article, the last available scientific literature regarding astaxhanthin chemistry, sources and its health effects are reviewed.

INTRODUCTION

Astaxanthin, a ketokaretenoid, belongs to the xanthophyll family and is the oxygenated derivatives of the quartetoids. Astaxanthin is found in natüre, especially around the sea. It is a pigment that gives red color to the meat of marine animals such as shrimp, lobster, crayfish and krill. Microalgae and phytoplankton also biosynthesize astaxanthin. Astaxanthin is found in microalgler *Haematococcus pluvialis*, *Chrolla zofingiensis* and *Chrolla zogingiensis* and *Chlorococcum sp.* and red yeast *Phaffa rhodozyma* and marine bacteria *Agrobacterium aurantiacum*(Yuan, Peng, Yin, and Wang, 2011). Astaxanthin can be used to give desired reddish –orange colour in the feed farm fish (Dose *et al*., 2016; Higuera-Ciapara, Felix-Valenzuela, and Goycoolea, 2006) In addition to being used as a coloring agent, astaxanthin plays role in inducing many antioxidant enzyme systems (Dose *et al*., 2016). In recent times, it is said that astaxanthin is about 100 times more potent than vitamin E against lipid peroxidation and about 40 times more effective than beta-carotene for singlet oxygen uptake (Yamashita, 2013). The structure of carotenoids is derived from lycopen. The majority is hydrocarbons of 40 carbon atoms and have 2 end ring systems linked by conjugated double bonds or the polyene system.Astaxanthin has both OH and Oxi group.

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Each double bonds in the polyene chain can be found in two different configurations, cis and trans. Cis isomer is thermodynamically less stabile but there is more trans isomere in nature. Astaxanthin is present in three configurations, 3R, 3 'R and 3S, 3'S and 3R, 3'S. Of all these isomers, 3S is the most abundant in nature, 3'S. Synthetic astaxanthines consist of 2 enantiomers and 1 mesoform, and three of the optical isomers are found in the shells (Higuera-Ciapara *et al*., 2006). Table 1 shows the percentage of configurational isomers in astaxanthin sources (Jackson, Braun, and Ernst, 2008).

The sources of astaxanthin

Synthetic astaxanthin is the same as living organisms and consists of a mixture of (3S, 3S), (3R, 3S) and (3R, 3R) isomers in 1: 2: 1 ratio, respectively. Only a few microbial origin green microalgae Haematococcus pluvialis, red yeast Phaffa rhodozyma can economically compete with synthetic astaxanthin. With improvements in photobioreactor technology production of astaxanthin from microalgler has earned commercial feasibility. It has been observed that the culture method develops between 1.5-3% astaxanthin on dry weight basis. Under controlled conditions, microalgae can be produced and processed by breaking down cell walls to increase carotenoid bioavailability. Finally tihsi biomass is dried and red powder is obtained. Many astaxanthin products are produced from H.pluvialis and is commercially selled (Higuera-Ciapara *et al*., 2006). The pigment from the red yeast

Phaffa rhodozyma is at a lower than H. Pluvialis (Çelikel, Kınık, Gönç, and Kavas). Table 2 shows astaxanthin percentages of astaxanthin sources (Biswal, 2014).

Table 1. Percentage of Configurational Isomers (%) *(Jackson et al.,* 2008)

Astaxanthin Sources	3S,3'S(%)	3R,3'R(%)	3R, 3'S(%)
Crustacyanine (Lobster)	33	39	28
Pfaffia rhodozyma(yeast)	-	100	-
Haematococcus pluvialis (algae)	99	-	-
Petals of Adonis anuua	100	-	-
Pandalus borealis(shrimp)	12-25	23-46	50-53
Salmo salar/Salmo (Atlantic/pasific salmon)	78-85	12-17	2-6

Table 2. Astaxanthin Percentages of Astaxanthin Sources (%)

Sources	Astaxanthin Percentage (%)
Salmon	5
Plankton	60
Krill	120
Shrimp	1200
Red Yeast *(P.rhodyzma*)	10.000
Heamatacoccus pluvialis	40.000

Chemical Structure

Astaxanthin has chiral center at 3 and 3' position(Dose *et al*., 2016). Free astaxanthin is prone to oxidation process. Therefore astaxanthin is present in nature in conjugated form to proteins or esterified with one or two fatty acids. Astaxanthin in H.pluvialis exists in many isomers esterified form. They are characterized according to the configuration of the two hydroxyl groups in the molecule. Esterification of hydroxyl groups increases hydrophobia and solution in globules made from triacylgliserols. Mostly they contain oleic acid(%51) and linoleic acid (Yuan *et al*., 2011). The chemical structure of the astaxanthin enantiomers is shown in Figure 1 (Caballero, Finglas, and Toldrá, 2015).

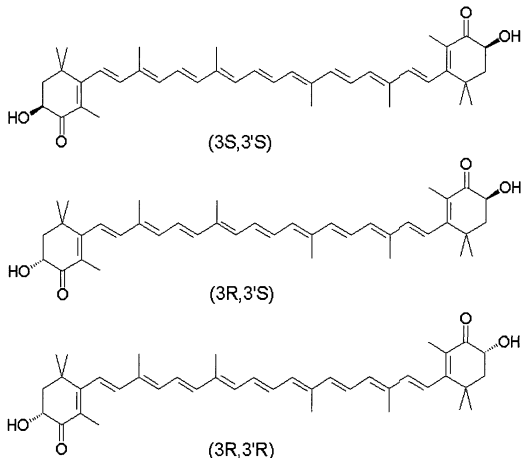

Figure 1. Chemical Structure of The Astaxanthin Enantiomers

Bioavailability and Safety

It is generally accepted that xantophyl esters have lower bioavailability. This issue is controversial. In humans, xanthophyll esters are hydrolyzed in the small intestines for absorption. The enzymatic esterification of xanthophylls begins after intestinal absorption. Esterified xanthophyll is placed in the lipid center of chylomicrons and transported to many tissues including the skin. By esterifying xanthophylls to less polar products, intestinal cells can protect against cytotoxic effects. The availability of astaxanthin in H. Pluvialis esters is an advantage for high bioavailability of astaxanthin (Yuan *et al*., 2011). According to one study, 40 mg astaxanthin per day for 4 weeks did not show any harmful effect (Kupcinskas *et al*., 2008). Even at very high doses, there is no toxic effect in animals and humans, but some people have reported orange color in their feces. This color is thought to have originated from the unabsorped astaxanthin (Biswal, 2014).In patients who are sensitive to seafood, hypoxia, deep pigmentation, extreme hair growth, hypocalcemia and decreased libido may occur in consumption of astaxanthin (Comhaire, Garem, Mahmoud, Eertmans, and Schoonjans, 2005). Astaxanthin, when it contacts with oxygen, will lose its utility and cause degredation. In this manner therapeutic effect of astaxanthin will also lose. Therefore, the necessity of paying attention to storage conditions of astaxanthin is emphasized (Biswal, 2014). According to EFSA reports, it was reported that when some nutrients were enriched with astaxanthin, they would be safe at most 4 mg or 0.1106 mg/kg per day. Reliable daily intake (ADI) in EFSA's FEEDAP panel was determined as 0.034 mg/kg (Efsa, 2015).

Effects on Health

Oxidative Stress: In contrast to β-carotene and lycopene astaxanthin is an antioxidant that has not pro-oxidant property. The non-polar carotenoids lycopene and beta-carotene disrupt the rich membrane layer of polyunsaturated fatty acids and show pro-oxidant action. Astaxanthin offers a 40% reduced lipid hydroperoxide level. Only astaxanthin from the carotenoids can effectively disrupt the apoptotic response to UV rays (Yamashita, 2013). Astaxanthin is a better free radical scavenger than the carotene carotenoids (Jackson *et al*., 2008). In a study in which ORAC values of some antioxidants were measured, myresitin 3,2 catechin 0.96, epicatechin 0,94, epigallocatechin gallate 1,13, resveratrol 0,64 astaxanthin 0,28 trolox equivalent was found (Sueishi *et al*., 2012). In a study comparing with the lipid peroxidation level control group, it was found that 250 mcg astaxanthin and astaxanthin esters were 5,2 and 2,8 fold in the group receiving and 100 mcg in the group receiving synthetic astaxanthin, respectively (Rao, Sarada, Shylaja, and Ravishankar, 2015).

Astaxanthin application prevents cell apoptosis, mitochondrial anomalies and the development of free oxygen species. It is also suggested that astaxanthin may be an effective treatment for oxidative stress-related neurodegenerative diseases (Osawa, 2012). Levels of SR-A and CD36 scavenger receptors responsible for the oxidation of LDL cholesterol may gradually decrease due to astaxanthin (Kishimoto *et al*., 2010). In addition, astaxanthin can capture diphenylpyrrolidone and galvonil free radicals, which cannot catch superoxide radicals (Dose *et al*., 2016). Finally, astaxanthin administration in rats with colon carcinogenesis has been shown to increase glutathione (GSH), vitamin C, and vitamin A levels in colon tissue. At the same time, superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx) and glutathione reductase (GR) enzyme levels were found to be higher in astaxanthin-given group (Prabhu, Ashokkumar, and Sudhandiran, 2009).

Antidiabetic Effect

Diabetes mellitus is associated with free radical production, a reduced antioxidant defense system and the resulting oxidative stress. Astaxanthin is thought to reduce oxidative stress leading to dysfunction of pancreatic cells (Yuan *et al*., 2011). Astaxanthin supplements has hypoglycemic and antihyperglycemic effects in diabetic rats (Kishimoto *et al*., 2010; Osawa, 2012; Prabhu *et al*., 2009). This significant fasting blood glucose decrease effect is explained by the stimulation of the pancreas mechanism. It is also reported that the antidiabetic effect of astaxanthin is due to its beneficial role in protecting pancreatic cells by inhibiting lipid peroxidation and capturing free radicals (Prabhu *et al*., 2009). In another study, rats are diveded into diabetic and healthy group. It is found that hyperglisemia is significantly lower in astaxanthin receiving diabetic group. In this study, plasma and renal melancholic MDA levels of the rats receiving astaxanthin diet decreased by 42% and 38%, respectively, and a significant decrease was found when compared with diabetic rats (Sila *et al*., 2015). Astaxanthin has been shown to improve many learning and memory parameters by preventing diabetic encephalopathy caused by hyperglycaemia in rats (Zhou *et al*., 2015). In a study of type 1 diabetic rats, astaxanthin at 50 mg/kg for 18 days prevented the formation of advanced glycation products (AGE) and reactive oxygen species due to hyperglycemia (C. H. Park *et al*., 2015). Insulin tolerance was found better in the astaxanthin group after 60 minutes of insulin injection compared to the control group in the patients with metabolic syndrome who received astaxanthin treatment. At the same time, blood glucose and blood insulin levels were reported to be better in the astaxanthin group (Hussein *et al*., 2007).

Cardiovascular Parameters

The development of atherosclerosis in humans has been associated with low-density lipoprotein (LDL). Higher levels of LDL increase the prevalence of cardiovascular disease. Oxidized LDL inhibition prevents the development of atherosclerosis. Astaxanthin inhibits LDL oxidation and prevents the development of cardiovascular diseases (Higuera-Ciapara *et al*., 2006). In a study investigating the effect of astaxanthin-enriched diet on blood pressure and cardiovascular parameters in hypertensive rats, it was revealed that astaxanthin has positive effects on many parameters. In another study, systolic blood pressure decreased in rats receiving 75 and 200 mg / kg astaxanthin, but only the systolic blood pressure of the control group was increased. In both astaxanthin-receiving groups, improvement in cardiachypertrophy is obtained and the antihypertensive effect was associated with antioxidant properties and decreased O2-production (Kimura *et al*., 2014). In rats given high-fat diets plus astaxanthin, free fatty acid levels were lower and HDL cholesterol was higher in the astaxanthin-receiving group (Yoshida *et al*., 2010). In a study of 41 men and 20 women with moderate hyperlipidemia, 12 weeks of astaxanthin treatment significantly lowered serum triglyceride levels and increased HDL cholesterol (Rao *et al*., 2015).

Liver Protective

Astaxanthin is transported to the liver by lipids and accumulates in the microsomal and mitochondrial fractions of the liver. Astaxanthin plays a protective role against chemicals such as CCl4 (Shen *et al*., 2014; Yuan *et al*., 2011). In a study 100 and 250 mcg/kg (14 Days) astaxanthin were found to have more positive effects on liver in rats given CCl4 toxin, astaxanthin and synthetic astaxanthin supplements, compared with the group receiving synthetic astaxanthin in the 250 mcg astaxanthin-treated group. Astaxanthin esters were also found to have higher liver protective properties in terms of liver enzymes, catalase, glutathione peroxidase, superoxide dismutase and lipid peroxidation. Astaxanthin administration in rats given CCl4 has helped maintain AST, ALT and ALP levels. Liver histopathology has returned to normal hepatic structure with minimal haemorrhage in rats given astaxanthin and synthetic astaxanthin following astaxanthin esters (Tripathi and Jena, 2010). In another study liver fibrosis was induced by administration of CCL4 to rats. Treatment with astaxanthin 40 mg/kg and 80 mg/kg improve the impaired levels of AST and ALT. However this improvement cannot seen with the dose of 20 mg/kg. At the same time the damages in liver were markedly reduced in liver by the astaxanthin (40 mg/kg and 80 mg/kg) (Shen *et al*., 2014).

Anticancer Effects

Astaxanthin has been shown to inhibit the development of many cancer cells such as colon, breast, prostate, etc. (Jyonouchi, Sun, Iijima, and Gross, 2000; Nakao *et al*., 2010). In a study cyclophosphamide (CP) induced oxidative stres rats, treatment with astaxanthin at 25 mg/kg before and after CP administration and recovery of malondealdehyde (MDA) and glutathione (GSH) levels is obtained disturbed by CP administration both before and after astaxanthin treatment provided. Liver cells morphology is destroyed in CP receiving group, while restoration of cellular morphology is provided by astaxanthin (Nakao *et al*., 2010). In a study conducted ın rats with breast tumors, the mean tumor development period was longer in the astaxanthin diet group compared to the control group and the tumor sizes were significantly smaller. Blood GSH concentration was found to be higher in the astaxanthin-receiving group when compared to the control group. At the same time, plasma IL-alpha levels were significantly lower in astaxanthin diet group (Jyonouchi *et al*., 2000). According to the results of the study in the rats given astaxanthin before and after the tumor was established, it was seen that in the astaxanthin given group 1 and 3 weeks before the tumor was given, there was significant decrease in tumor size and weight (Ikeuchi, Koyama, Takahashi, and Yazawa, 2007).

Obesity

According to a study of rats given high-fat diet plus astaxanthin, it is found that 30 mg/kg/day astaxanthin treatment when compered with high fat diet adipose tissue acquisition is significantly lower. The administration of 1,2 mg/kg/day and 6 mg/kg/day showed a tendency to decrease adipose tissue weight (Yang *et al*., 2014). In another study adiposit size was found to be smaller in astaxanthin-receiving group in rats given high-fat diets plus astaxanthin (21). In rats receiving high fat diet plus 0.03% astaxanthin, high-fat diets were found to have an increased rate of high epididymal adipose tissue (Aoi *et al*., 2008).

Physical Activity Durability: In mammals, astaxanthin accumulates in the muscle as well as in the liver. In prolonged

exercises astaxanthin prevents muscles from destrecution and peroksidation of DNA and lipids (Polotow *et al*., 2014). In a study 6mg/kg and 30 mg/kg astaxanthin was applied to rats performed swimming activity. It is found that pro-exercise fatigue occured late in the group receving astaxanthin. All astaxanthin receiving groups lactate levels are significantly lower than group without astaxanthin. In a group receiving 30 mg/kg astaxanthin it is found that glycogen levels in the liver is higher than control group. Creatin kinase levels which increases with exercise, is found lower in the groups receiving astaxanthin (Yang *et al*., 2014). In another study compared with the control group in astaxanthin-treated rats, the fatigue time in the swimming activity process was found to be 29% longer (Earnest, Lupo, White, and Church, 2011). In a study of male subjects aged 18-39 years, bicycle time test performance was measured and administered encapsulated astaxanthin 4 mg/day for 28 days and astaxanthin group showed significant improvement in cycling performance compared to group receiving placebo. At the same time in the group receiving astaxanthin was found to be significantly higher in power measurements (Sawaki *et al*., 2002). In another study, astaxanthin supplementation in 18 healthy male subjects was found to have a decreasing effect of lactic acid concentration 2 minutes after exercise (Liu *et al*., 2014).

In rats given astaxanthin with exercise, non-esterified fatty acid levels decreased. At the same time, in sedanter conditions this levels showed tendency to decrease. The decline in pH levels after exercise was supressed. Astaxanthin uptake activated the aerobic metabolism of mitochondria by significantly increasing levels of peroxisome proliferator-activating receptor coactivator 1 alpha (PGC-1ALFA).Thus it is determined that the utilisation of lipids increased (Ohgami *et al*., 2003).

Inflamation and Immune Response

It is thought that the potential mechanism for astaxanthin's antiinflammatory effect is caused by blocking the nitric oxide synthase enzyme system directly Mean 21-year-old female subjects randomized to 0-2-8 mg/day astaxanthin for 8 weeks for double blind study. It is found that 2 mg/kg astaxanthin treatment provided lower levels of C- reactive protein. Astaxanthin intake on diet increased T and B cell populations by increasing natural killer cell cytotoxic activity (J. S. Park, Chyun, Kim, Line, and Chew, 2010).

Helycobacter Pylori Infecton

Helicobacter pylori infection has been associated with reduced levels of antioxidants. Antioxidant properties of Astaxanthin are thought to be a new strategy in the treatment of helicobacter pylori. In a study with Helicobacter pylori infection, 100 mg/day astaxanthin supplementation reduced H.pylori infection and lipid peroxidation levels in the gastric mucosa of rats were significantly lower in astaxanthin treated group (Wang, Willén, and Wadström, 2000). In another study conducted in individuals with H.pilori positive, inflammation also decreased in the astaxanthin-administered group and in the control group. In the group receiving 40 mg astaxanthin per day, the levels of CD4 and CD8, which are gastric inflammatory markers, decreased significantly (Andersen *et al*., 2007).

Neurodegenerative Diseases

In a study of subarachnoid hemorrhagic rats 25 mg and 75 mg/day astaxanthin supplementation was performed. Seventy five mg/day astaxanthin was reported to help relieve brain edema, improve blood-brain barrier, and improve neurological dysfunction. However, 25 mg/day astaxanthin administration did not cause a significant difference. It is emphasized that astaxanthin helped prevention of neural degeneration resulting from subarachnoid haemorrhage (Zhang *et al*., 2014). In another study aging process was performed in brain of rats. Astaxanthin treatment decreased 8-hydroxy-2-deoxiguanosine (8-OHdg) levels and decreased protein carbonylation levels in brains of rats. Brain GSH and SOD levels were significantly higher in astaxanthin receiving group (Wu *et al*., 2014).

Conclusion

As a result of metabolic events in the body, reactive oxygen species come into play. They play a role in disease development in many tissues and organs in the body. Free radicals have major effects in the development of diseases such as cardiovascular diseases, diabetes, cancer, liver diseases. The antioxidant defense system has a fairly large precaution for eliminating the effects of these substances. The antioxidant properties of astaxanthin are higher when compared to other carotenoids. DNA damage, disease progression, lipid peroxidation, apoptosis of cells can be reduced with the effects of astaxanthin. Astaxanthin has many positive effects because it is an antioxidant without prooxidant effect. The use of antioxidants as a supplement is becoming more and more popular day by day. In this way there are reinforcements offered to the consumer for use. However, the consumption of foods containing astaxanthin should be prioritized by following healthy eating principles.

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