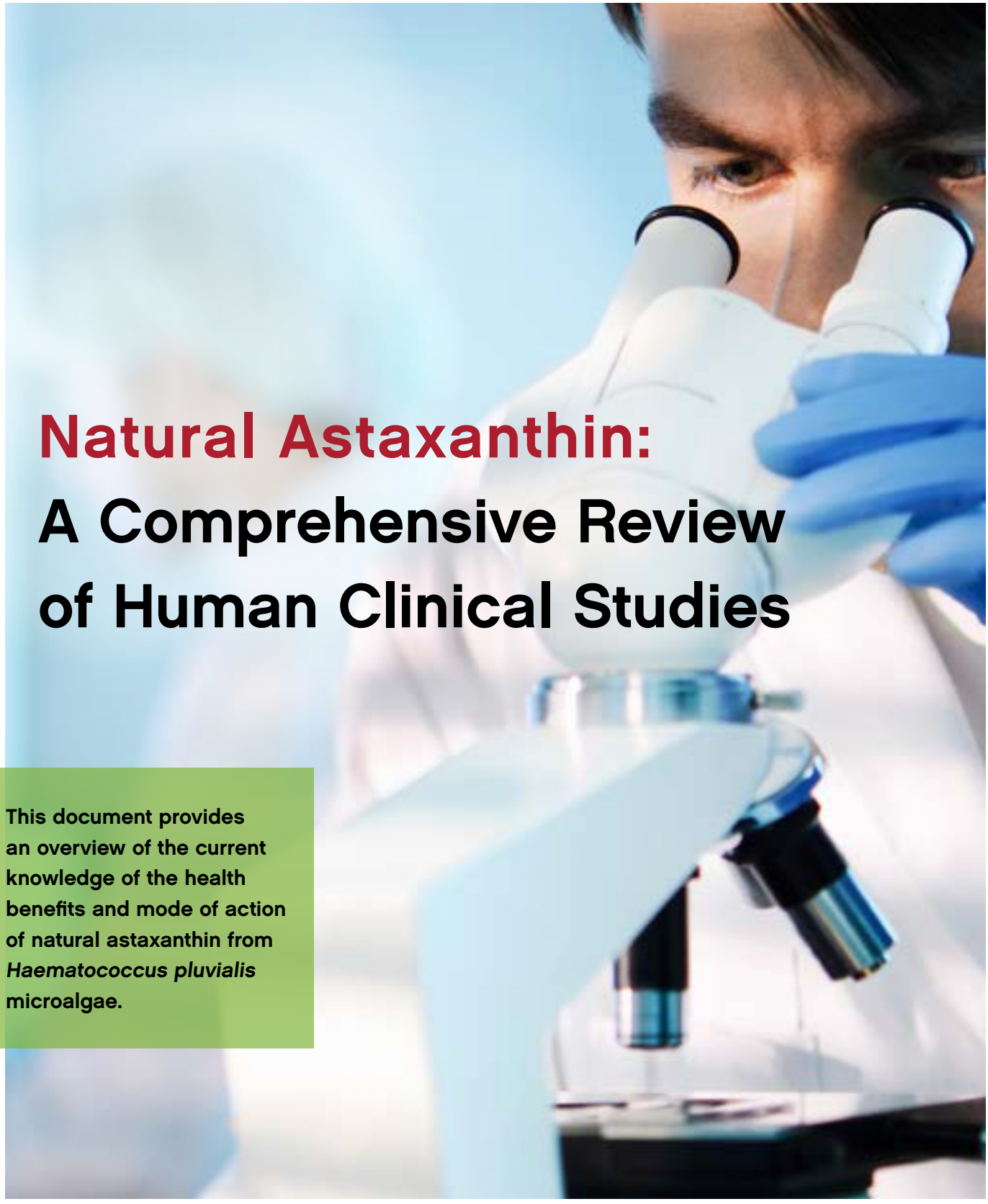

Natural Astaxanthin:
A Comprehensive Review of Human Clinical Studies

This document provides an overview of the current knowledge of the health benefits and mode of action of natural astaxanthin from *Haematococcus pluvialis* microalgae.

Issue date: 04 September 2017
Issue number: 3
Supersedes date: 10 March 2017

algalif® Iceland inside™

Contents

For further information, please contact the **Algalif Global Sales Office** at **+47 21 95 12 00** or email us at **sales@algalif.com.**

1 Introduction

A prominent consequence of modern lifestyles is the increased generation of free radicals because of an unhealthy diet, extensive sunbathing, exposure to pollutants, a sedentary lifestyle, stress, and the use of drugs to temporarily minimize the symptoms of chronic health ailments. Excess free radicals may overcome natural cellular antioxidant defenses, leading to oxidation and damage to vital cellular components. Moreover, our body accumulates oxidative damage as we age, and our growing aging population is more susceptible to certain health conditions associated with oxidative stress.

Several decades of dietary research findings suggest that consuming greater amounts of antioxidant-rich foods might help people to stay healthy. These results have provoked significant interest in antioxidant supplements. Dietary supplementation with antioxidants is receiving growing attention and is increasingly adopted in Western countries. Among antioxidants, natural astaxanthin stands out for its exceptional antioxidant capabilities.

Astaxanthin belongs to a family of naturally-occurring organic pigments called carotenoids. There are over six hundred known carotenoids, such as lycopene, lutein, and β-carotene. They are responsible for the bright red, yellow, and orange colors of many fruits and vegetables. Astaxanthin is the main carotenoid in aquatic animals such as shrimps, lobsters, salmon, trout, and red seabream, and contributes to the pinkish-red color of their flesh. Astaxanthin is also found in some birds, such as the flamingo.

The green microalgae, *Haematococcus pluvialis (H. pluvialis)*, produce the red pigment astaxanthin as a protection against environmental stress factors such as UV-radiation and depletion of nutrients [1]. The microalgae synthesizes the highest amount of astaxanthin in nature, which makes it the first choice for the commercial production of natural astaxanthin for dietary supplements and functional foods.

2 Astaxanthin as an Antioxidant

Natural astaxanthin is a powerful antioxidant and neutralizes free radicals. The health benefits of natural astaxanthin can be explained by understanding how an antioxidant works.

The primary function of antioxidants in the human body is to protect our cells against free radicals, such as reactive oxygen species (ROS). Free radicals are unstable molecules that damage or “oxidize” cells and tissues in a process called oxidative stress. Free radical formation occurs continually in our body:

- ROS are formed as a by-product during normal metabolic processing in our body when food, which serves as fuel, is converted into energy to run cellular processes.
- ROS are released by immune cells to fight bacterial infections.
- ROS are also generated by lifestyle factors such as exposure to pollutants, an unhealthy diet, excessive sun bathing, heavy exercise, smoking, etc.

Astaxanthin is a potent antioxidant and offers protection against free radical damage to preserve healthy lipids, proteins, and DNA, and help the human body maintain a healthy state. To maintain the balance, a continual supply of antioxidants in the diet is necessary.

The formation of the potentially harmful ROS by-products often involves chain reactions that increase in extent if they are not stopped. It is estimated that each cell forms more than 20 trillion ROS per day through normal metabolism, and each cell is believed to be attacked by these reactive molecules 10,000 times per day [2]. Oxidative stress occurs when more ROS are generated than the body's natural defense mechanism can counteract. This damages cellular structures, lipids, proteins, and genetic material (DNA).

• Membrane **lipid oxidation** leads to loss of membrane fluidity and elasticity, impaired cellular functioning, and even cell rupture. Oxidative degradation of lipids is responsible for lipid rancidity, loss of function, and generation of some toxic products. A variety of lipid breakdown products may bind cell receptors and initiate signaling pathways. In many cases, this leads to pro-inflammatory processes.

• **Protein oxidation** can cause fragmentation of amino acid residues, the formation of protein-protein cross-linkages, and protein backbone oxidation, which ultimately leads to loss of function. Damaged proteins affect intracellular signaling pathways and are contributing factors to different disorders.

• **DNA oxidation** causes alterations in DNA bases. If left unrepaired, the modifications of DNA bases can lead to genetic defects, and accelerate physiological decline and the development of age-related diseases.

Over time, oxidative stress can leave our cells and tissues unable to function properly, contributing to premature aging. Moreover, our bodies accumulate oxidative damage as we age and we become more susceptible to chronic disorders.

An antioxidant is a molecule stable enough to donate an electron to a free radical and neutralize it, thus reducing its capacity to damage. Antioxidants delay or inhibit cellular damage mainly through their free radical scavenging property. Dietary intake is an important source of antioxidants.

Natural astaxanthin is considered a "super antioxidant" and possesses one of the strongest known antioxidant effects. Astaxanthin consists of two terminal rings joined by a polyene chain (Fig. 1 A). While structurally similar to the carotenoid β-carotene, astaxanthin has thirteen conjugated double bonds whereas β-carotene has eleven. On cyclohexene structure, it has oxo groups in the 4 and 4 prime positions that increase its antioxidant potential. Additionally, astaxanthin has hydroxyl groups at the 3 and 3 prime position, making the molecule somewhat polar. Because of its unique structure, particularly all the unsaturated bonds and the oxo-groups in both ends, astaxanthin can trap harmful radicals effectively. Comparison studies have shown that natural astaxanthin is six thousand times more capable than vitamin C, one hundred times more powerful than vitamin E, and five times more powerful than β-carotene in trapping energy from singlet oxygen, a common free radical in biological systems [3] (Fig. 1 B). Astaxanthin can also trap many different types of radicals. In addition, the way astaxanthin neutralizes harmful free radicals is gentle to the body's cells. Other antioxidant mechanisms can be harmful since they turn the antioxidant itself into highly reactive molecules [4].

A. Structural Formula of Natural Astaxanthin (S, S´ isomer)

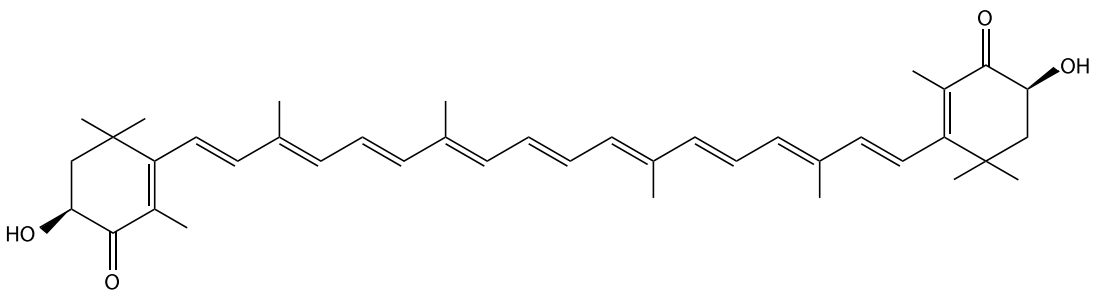

Figure 1 A. *Astaxanthin consists of two terminal rings joined by a polyene chain.*

B. Natural Astaxanthin is Stronger Than Other Antioxidants

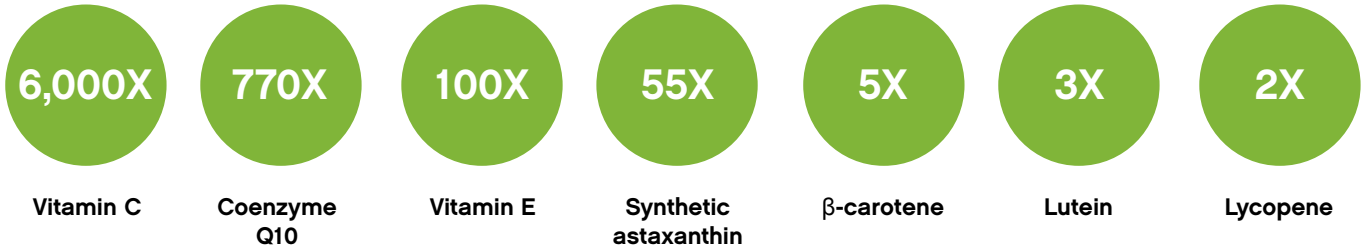

Figure 1 B. *Natural astaxanthin is more powerful than other antioxidants in trapping energy from free radicals, such as singlet oxygen (1O2) [3, 5].*

3 Safety and Bioavailability

Astaxanthin has a long history of use in the human diet as a naturally occurring component of foods. In addition, dry meals of *Haematococcus pluvialis* has been marketed as a dietary supplement in the United States since at least 1999 [6].

There is sufficient qualitative and quantitative scientific evidence, including human and animal data, to support the safety of natural astaxanthin [7-10]. No side effects have been reported for astaxanthin and *Haematococcus pluvialis* extract characterized by component astaxanthin esters of common edible fatty acids [11].

A significant body of scientific evidence including human and animal studies supports the safety of natural astaxanthin derived from *Haematococcus pluvialis.*

Haematococcus pluvialis extract characterized by component astaxanthin esters has been awarded a GRAS (Generally Regarded As Safe) classification by the United States Food and Drug Administration (FDA). It allows the use of astaxanthin esters from *Haematococcus pluvialis* as a food additive for baked goods and baking mixes, beverages and beverage bases, energy, sports, and isotonic drinks, non-milk-based meal replacements, cereals and cereal products, chewing gums, coffee, tea, dairy product analogs, frozen dairy desserts and mixes, hard and soft candy, milk products, processed fruits and fruit juices, and processed vegetables and vegetable juices at a maximum level of 0.15 mg astaxanthin per serving [11]. The recommended daily dose of natural astaxanthin as a dietary supplement ranges from 2 mg to 12 mg, depending on local regulations [12, 13].

When taken as a dietary supplement or consumed with foods rich in carotenoids, astaxanthin is absorbed along with dietary lipids through passive diffusion into intestinal cells. Through multiple digestive actions, astaxanthin is incorporated like other carotenoids into lipoproteins and secreted back into the circulation for delivery to the tissues [14]. The bioavailability and distribution of astaxanthin has been studied in humans using single doses of 40 mg up to 100 mg with maximum concentrations in the blood observed between 7 h and 21 h and ranging from 0.055 to 1.3 mg/L [10, 15, 16]. The reported elimination half-life of astaxanthin from the blood is approximately 16 h [16].

Bioavailability and distribution in plasma depend on a variety of factors, such as fractions of free and esterified astaxanthin, the proportion of isomers, formulation (e.g. co-administration of fat or surfactants), and application (e.g. with or without meals) or smoking habits (Table 1).

Table 1. Factors Influencing Astaxanthin Bioavailability		
	Astaxanthin Bioavailability	**Ref.**
Consumption	The bioavailability of astaxanthin was 2.4 times higher in the after-meal group than in the before-meal group. Therefore, astaxanthin should be consumed with some dietary fat for optimal absorption.	[10]
Formulation	Lipid-based formulations may enhance astaxanthin bioavailability approximately two to four times.	[16]
Isomers	Isomers Astaxanthin exists in different optical and configurational stereoisomers. Stereoisomerism exerts a marked influence on the physical properties, which have been studied mainly in animal models. This is because the natural astaxanthin in the human diet comes mainly from microalgae or wild salmonids that feed on algae, and has the same composition of isomers. Isomeric distribution in natural astaxanthin differs from that of the synthetic product. The naturally occurring S, S´ isomer of astaxanthin accumulates selectively in plasma because of the stereospecific hydrolysis of the 3 and 3´-hydroxy groups. A characteristic distribution of astaxanthin optical isomers reflecting the feed ingredient was detected in the flesh of farmed trout, meaning that salmonids cannot convert astaxanthin isomeric forms. Similarly, the intestinal absorption of configurational 9Z– and 13Z-astaxanthin is lower than for the all-*E* isomer. Moreover, the all-*E*-isomer accumulates selectively in muscle and plasma, and the 13Z-astaxanthin isomer in the liver of farmed salmonid fishes.	[15, 17-20]
Esterification	Natural astaxanthin from *Haematococcus pluvialis* is esterified and, because of this, is more stable and more easily absorbed into the body. The unesterified astaxanthin form is extremely sensitive to oxidation.	[21-23]
Other	Tobacco smoke promotes astaxanthin degradation leading to reduced bioavailability.	[10]

4 Overview of Human Clinical Studies Using Astaxanthin

Astaxanthin has been studied by research groups worldwide and is recognized as safe and effective. The number of scientific studies on natural astaxanthin is rapidly growing and solid documentation is available for several diverse applications. There are over fifty published clinical studies on astaxanthin in humans, as well as many *in vitro* and *in vivo* studies (Fig. 2 A).

Astaxanthin provides various human health benefits. Effects of astaxanthin are reported in human clinical studies and further supported by studies *in vitro* and in animal models.

In clinical studies, astaxanthin has been mainly used as a single component (80%), although studies with astaxanthin in combination with other nutrients are also available (20%) (Fig. 2 B). A thorough examination of astaxanthin sources used in these studies revealed that natural astaxanthin was largely obtained from *Haematococcus pluvialis* (97%) (Fig. 2 C). This provides evidence that astaxanthin from algal sources is the best documented when it comes to health benefits.

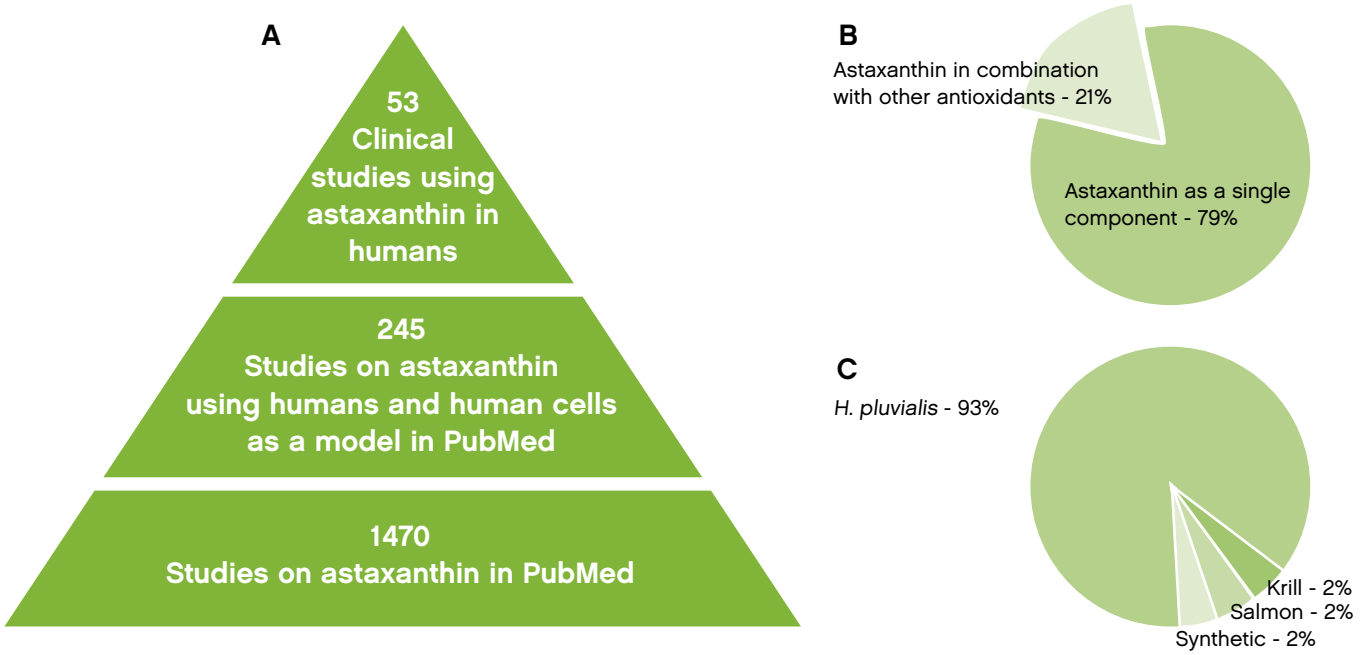

Figure 2.

Overview of research studies on astaxanthin.

A. *The total number of studies on astaxanthin in PubMed, including studies in-vitro and using animal models (search performed on 2016-11-17).*

B. *Clinical studies in which astaxanthin was used as a single component (n=42) or in combination (n=11) with other dietary supplements such as other antioxidants.*

C. *Distribution of astaxanthin sources in clinical studies (microalgae Haematococcus pluvialis, n=39; krill, n=1; synthetic astaxanthin, n=1; salmon, n=1).*

5 Health Benefits Supported by Clinical Studies with Astaxanthin from *Haematococcus Pluvialis*

The following health benefits for **natural astaxanthin from *Haematococcus pluvialis*** have been demonstrated by clinical studies:

- **Promotes healthy oxidative balance;**
- **Supports cardiovascular health;**
- **Supports healthy skin;**
- **Supports healthy aging;**
- **Supports the body's recovery from heavy exercise.**

Natural astaxanthin reduces oxidative stress and helps the human body maintain a healthy state. It is beneficial for a wide range of individuals.

Research on the health effects of astaxanthin has focused mainly on its antioxidant properties and protective effects against oxidative stress when used as a dietary supplement. Such studies have identified the relationship between the supplemented dose and observed beneficial health effects. A growing body of clinically validated evidence indicates the benefits of natural astaxanthin in a range of target groups, including young, highly-trained athletes and healthy middle-aged and senior subjects. A comprehensive summary of clinical studies using natural astaxanthin from *Haematococcus pluvialis* is given in Appendix Table 1.

5.1 Promotes Healthy Oxidative Balance

The state of balance between free radical generation and the protection capacity of an endogenic antioxidant defense is called oxidative equilibrium. In this state, the body's tissues and cells are maximally protected against toxic oxidative influences. When the oxidative balance is disturbed, the cellular components are not protected against oxidative radical effects because of the impaired relationship between the activity and the intracellular levels of endogenic antioxidants and prooxidants, which can result in toxic damage, disease, and premature aging.

The unique chemical structure of astaxanthin makes it a potent antioxidant. The mode of action of astaxanthin is grounded in its ability to keep oxidative equilibrium, neutralize radicals, and prevent damage. Astaxanthin benefits for healthy oxidative balance at a glance are given in Table 2.

Table 2. Astaxanthin Benefits for Healthy Oxidative Balance

Dietary supplementation with astaxanthin	• Reduces oxidative stress; • Stimulates activity of the body's own antioxidant system; • Decreases inflammation and enhances immune responses.
Dose	2, 6, 8, 12 or 20 mg/day* **Doses up to 40 mg/day were used, however there were no significant differences between 5, 20 or 40 doses of astaxanthin on the beneficial effect or level of astaxanthin in blood [24].*
Time-to-effect	From 3 to 12 weeks
Gender	Females, males
Age	18-70
Markers of the effectiveness	• Oxidative stress biomarkers, such as malondialdehyde, isoprostane. • Antioxidant system biomarkers, such as superoxide dismutase, total antioxidant capacity. • Complete blood cell count and basic metabolic panel, including C-reactive protein, cholesterol, and triglycerides, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, apolipoprotein A1, and apolipoprotein B; • Immune cell subpopulations and inflammatory cytokines in the blood.

5.1.1 Studies Focused on Astaxanthin and Oxidative Balance

Kim et al. (2011). "Protective effects of Haematococcus astaxanthin on oxidative stress in healthy smokers." J Med Food 14(11): 1469-1475. [24]

"Free radicals induced by cigarette smoking have been strongly linked to increased oxidative stress in vivo, contributing to the pathobiology of various diseases. This study was performed to investigate the effects of *Haematococcus astaxanthin* (ASX), which has been known to be a potent antioxidant, on oxidative stress in smokers. Thirty-nine heavy smokers (>/=20 cigarettes/day) and 39 non-smokers were enrolled in this study. Smokers were randomly divided into three dosage groups to receive ASX at doses of 5, 20, or 40 mg (n=13, each) once daily for 3 weeks. Oxidative stress biomarkers such as malondialdehyde, isoprostane, superoxide dismutase, and total antioxidant capacity, and ASX levels in plasma were measured at baseline and after 1, 2, and 3 weeks of treatment. Compared with baseline, the plasma malondialdehyde and isoprostane levels decreased, whereas superoxide dismutase level and total antioxidant capacity increased in all ASX intervention groups over the 3-week period. In particular, isoprostane levels showed a significant dose-dependent decrease after ASX intake. The results suggest that ASX supplementation might prevent oxidative damage in smokers by suppressing lipid peroxidation and stimulating the activity of the antioxidant system in smokers."

Choi et al. (2011). "Effects of astaxanthin on oxidative stress in overweight and obese adults." Phytother Res 25(12): 1813-1818. [25]

"Oxidative stress is caused by an imbalance between the antioxidant and the reactive oxygen species, which results in damage to cells or tissues. Recent studies have reported that oxidative stress is involved in obesity, in addition to many other human diseases and aging. A prospective, randomized, double-blind study was performed to investigate the effect of astaxanthin (ASX), which is known to be a potent antioxidant, on oxidative stress in overweight and obese adults in Korea. Twenty-three adults with BMI > 25.0 kg/m(2) enrolled in this study and were randomly assigned to two dose groups: ASX 5 mg and 20 mg once daily for 3 weeks. Malondialdehyde (MDA), isoprostane (ISP), superoxide dismutase (SOD) and total antioxidant capacity (TAC), as oxidative stress biomarkers, were measured at baseline and 1, 2 and 3 weeks after ASX administration. Compared with baseline, the MDA (by 34.6% and 35.2%) and ISP (by 64.9% and 64.7%) levels were significantly lowered, whereas SOD (by 193% and 194%) and TAC (by 121% and 125%) levels were significantly increased in two dose groups after the 3 week intervention. This study revealed that supplemental ASX for 3 weeks improved oxidative stress biomarkers by suppressing lipid peroxidation and stimulating the activity of the antioxidant defense system."

Park et al. (2010). "Astaxanthin decreased oxidative stress and inflammation and enhanced immune response in humans." Nutr Metab (Lond) 7: 18. [26]

"BACKGROUND: Astaxanthin modulates immune response, inhibits cancer cell growth, reduces bacterial load and gastric inflammation, and protects against UVA-induced oxidative stress in in vitro and rodent models. Similar clinical studies in humans are unavailable. Our objective is to study the action of dietary astaxanthin in modulating immune response, oxidative status and inflammation in young healthy adult female human subjects. METHODS: Participants (averaged 21.5 yr) received 0, 2, or 8 mg astaxanthin (n = 14/diet) daily for 8 wk in a randomized double-blind, placebo-controlled study. Immune response was assessed on wk 0, 4 and 8, and tuberculin test performed on wk 8. RESULTS: Plasma astaxanthin increased (P < 0.01) dose-dependently after 4 or 8 wk of supplementation. Astaxanthin decreased a DNA damage biomarker after 4 wk but did not affect lipid peroxidation. Plasma C-reactive protein concentration was lower (P < 0.05) on wk 8 in subjects given 2 mg astaxanthin. Dietary astaxanthin stimulated mitogen-induced lymphoproliferation, increased natural killer cell cytotoxic activity, and increased total T and B cell subpopulations, but did not influence populations of T-helper, T-cytotoxic or natural killer cells. A higher percentage of leukocytes expressed the LFA-1 marker in subjects given 2 mg astaxanthin on wk 8. Subjects fed 2 mg astaxanthin had a higher tuberculin response than unsupplemented subjects. There was no difference in TNF and IL-2 concentrations, but plasma IFN-gamma and IL-6 increased on wk 8 in subjects given 8 mg astaxanthin. CONCLUSION: Therefore, dietary astaxanthin decreases a DNA damage biomarker and acute phase protein, and enhances immune response in young healthy females."

5.1.2 Supporting Studies on Astaxanthin and Oxidative Balance

Baralic et al. (2015). "Effect of Astaxanthin Supplementation on Salivary IgA, Oxidative Stress, and Inflammation in Young Soccer Players." Evid Based Complement Alternat Med 2015: 783761. [27]

The study focused on oxidative stress in athletes. An abstract is given under Exercise Recovery.

Choi et al. (2011). "Positive effects of astaxanthin on lipid profiles and oxidative stress in overweight subjects." Plant Foods Hum Nutr 66(4): 363-369. [28]

The study focused on lipid profiles in blood and oxidative stress. An abstract is given under Cardiovascular Health.

Hashimoto et al. (2013). "Effects of astaxanthin on antioxidation in human aqueous humor." J Clin Biochem Nutr 53(1): 1-7. [29]

The study focused on age-related vision degeneration and oxidative stress in the aqueous humor. An abstract is given under Healthy Aging.

Iwabayashi et al. (2009). "Efficacy and safety of eight-week treatment with astaxanthin in individuals screened for increased oxidative stress burden." Anti-Aging Med 6(4): 15-21. [30]

The study was an open-label noncontrolled study in subjects with increased oxidative stress. Results show that dietary astaxanthin supplementation had multiple positive effects.

Yamada et al. (2010). "Evaluation of therapeutic effects of astaxanthin on impairments in salivary secretion." J Clin Biochem Nutr 47(2): 130-137. [31]

This was a pilot study on individuals with impaired salivary secretion and provided evidence that dietary astaxanthin reduced oxidative stress markers in saliva.

5.2 Supports Cardiovascular Health

The circulatory or cardiovascular system is made up of blood, blood vessels, and the heart. It is an important transportation system that carries nutrients within the body, while it collects waste products and transports them to the body's waste stations such as the kidneys, liver, and lungs.

Sugar levels, as well as the amount/type of fat in the blood, are factors that can affect circulation. Free radicals may oxidize the fat in the blood, thereby contributing to adverse cardiovascular conditions. Clinical studies demonstrate that astaxanthin supplements can prevent oxidative damage of fat particles in the blood, improve lipid profiles, and promote better blood flow in capillaries. Astaxanthin benefits for cardiovascular health at a glance are given in Table 3.

Table 3. Astaxanthin Benefits for Cardiovascular Health	
Dietary supplementation	• Reduces oxidative stress; • Improves lipid profiles, decreased triglyceride-rich lipoproteins; • Promotes better blood flow in capillaries.
Dose	6, 8, 12 or 18 mg /day
Time-to-effect	From 4 to 48 weeks
Gender	Females, males
Age	19-70
Markers of the effectiveness	• Blood cell count and basic metabolic panel, including plasma glucose, fatty acids, triglyceride, serum total cholesterol, LDL-cholesterol, HDL-cholesterol, serum adiponectin. • Rheology evaluations/blood flow velocity (flow properties of blood and its elements). • Endogenous antioxidants, such as paraoxonase. • Inflammation markers, such as interleukin 6 and interleukin 2 receptors and plasma protein C.

5.2.1 Studies Focused on Astaxanthin Benefits for Cardiovascular Health

Yoshida et al. (2010). "Administration of natural astaxanthin increases serum HDL-cholesterol and adiponectin in subjects with mild hyperlipidemia." Atherosclerosis 209(2): 520-523. [32]

"BACKGROUND: Astaxanthin has been reported to improve dyslipidemia and metabolic syndrome in animals, but such effects in humans are not well known. METHODS: Placebo-controlled astaxanthin administration at doses of 0, 6, 12, 18 mg/day for 12 weeks was randomly allocated to 61 non-obese subjects with fasting serum triglyceride of 120-200mg/dl and without diabetes and hypertension, aged 25-60 years. RESULTS: In before and after tests, body mass index (BMI) and LDL-cholesterol were unaffected at all doses, however, triglyceride decreased, while HDL-cholesterol increased significantly. Multiple comparison tests showed that 12 and 18 mg/day doses significantly reduced triglyceride, and 6 and 12 mg doses significantly increased HDL-cholesterol. Serum adiponectin was increased by astaxanthin (12 and 18 mg/day), and changes of adiponectin correlated positively with HDL-cholesterol changes independent of age and BMI. CONCLUSIONS: This first-ever randomized, placebo-controlled human study suggests that astaxanthin consumption ameliorates triglyceride and HDL-cholesterol in correlation with increased adiponectin in humans."

Karppi et al. (2007). "Effects of astaxanthin supplementation on lipid peroxidation." Int J Vitam Nutr Res 77(1): 3-11. [33]

"Astaxanthin, the main carotenoid pigment in aquatic animals, has greater antioxidant activity in vitro (protecting against lipid peroxidation) and a more polar configuration than other carotenoids. We investigated the effect of three-month astaxanthin supplementation on lipid peroxidation in healthy non-smoking Finnish men, aged 19-33 years by using a randomized double-blind study design. Also absorption of astaxanthin from capsules into bloodstream and its safety were evaluated. The intervention group received two 4-mg astaxanthin (Astaxin) capsules daily, and the control group two identical-looking placebo capsules. Astaxanthin supplementation elevated plasma astaxanthin levels to 0.032 pmol/L ($p < 0.001$ for the change compared with the placebo group). We observed that levels of plasma 12- and 15-hydroxy fatty acids were reduced statistically significantly in the astaxanthin group ($p = 0.048$ and $p = 0.047$ respectively) during

supplementation, but not in the placebo group and the change of 15-hydroxy fatty acid was almost significantly greater (p = 0.056) in the astaxanthin group, as compared with the placebo group. The present study suggests that intestinal absorption of astaxanthin delivered as capsules is adequate, and well tolerated. Supplementation with astaxanthin may decrease in vivo oxidation of fatty acids in healthy men."

Choi et al. (2011). "Positive effects of astaxanthin on lipid profiles and oxidative stress in overweight subjects." Plant Foods Hum Nutr 66(4): 363-369. [28]

"Astaxanthin, a carotenoid, has antioxidant activity as well as many positive effects, such as anticancer and anti-inflammatory effects. We performed a randomized, double-blind, placebo-controlled study to investigate the effects of astaxanthin on lipid profiles and oxidative stress in overweight and obese adults in Korea. In total, 27 subjects with body mass index >25.0 kg/m(2) were enrolled and randomly assigned into two groups administered astaxanthin or placebo capsules for 12 weeks. Total cholesterol, triglycerides, high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol, apolipoprotein A1 (ApoA1), and apolipoprotein B (ApoB) were measured before and after intervention. Malondialdehyde (MDA), isoprostane (ISP), superoxide dismutase (SOD), and total antioxidant capacity (TAC), as oxidative stress biomarkers, were measured at baseline and at 4, 8, and 12 weeks after intervention. LDL cholesterol and ApoB were significantly lower after treatment with astaxanthin, compared with the start of administration, whereas none of the lipid profiles was changed in the placebo group. At the baseline, all four biomarkers were not significantly different between the two groups. Compared with the placebo group, MDA and ISP were significantly lower, but TAC was significantly higher in the astaxanthin group at 12 weeks. These results suggest that supplementary astaxanthin has positive effects by improving the LDL cholesterol, ApoB, and oxidative stress biomarkers."

Miyawaki et al. (2008). "Effects of Astaxanthin on Human Blood Rheology." Journal of Clinical Biochemistry and Nutrition 43(2): 69-74. [34]

"Effects of astaxanthin (AX) derived from *H. pluvialis* on human blood rheology were investigated in 20 adult men with a single-blind method. The experimental group was 57.5 ± 9.8 years of age and the placebo group was 50.8 ± 13.1 years of age. A blood rheology test that measures whole blood transit time was conducted using heparinized blood of the volunteers by a MC-FAN apparatus (microchannel array flow analyzer). After administration of AX 6 mg/day for 10 days, the values of the experimental group were decreased from 52.8 ± 4.9 s to 47.6 ± 4.2 s ($p<0.01$) and a comparison of the values between the experimental (47.6 ± 4.2 s) and the placebo (54.2 ± 6.7 s) groups showed a significant difference ($p<0.05$). There were no adverse effects resulting from the administration of AX 6 mg/day for 10 days. Informed consent was obtained from each subject."

5.2.2 Supporting Studies on Astaxanthin and Cardiovascular Health

Iwabayashi et al. (2009). "Efficacy and safety of eight-week treatment with astaxanthin in individuals screened for increased oxidative stress burden." Anti-Aging Med 6(4): 15-21. [30]

The study was an open-label noncontrolled study in subjects with increased oxidative stress. Results show that dietary astaxanthin supplementation had multiple positive effects.

Kim et al. (2004). "The Effects of Astaxanthin Supplements on Lipid Peroxidation and Antioxidant Status in Postmenopausal Women." Nutritional Sciences 7(1): 41-46. [35]

The study focused on age-related blood lipid peroxidation and antioxidant status in postmenopausal women. An abstract is given under Healthy Aging.

Nakagawa, K., et al. (2011). "Antioxidant effect of astaxanthin on phospholipid peroxidation in human erythrocytes." Br J Nutr 105(11): 1563-1571. [36]

The study focused on blood lipid peroxidation and antioxidant status in healthy middle-aged and senior subjects. An abstract is given under Healthy Aging.

Saito et al. (2012). "Astaxanthin increases choroidal blood flow velocity." Graefes Arch Clin Exp Ophthalmol 250(2): 239-245. [37]

The study focused on blood flow in eye capillaries in relation to age-related oxidative stress. An abstract is given under Healthy Aging.

5.3 Supports Healthy Skin

The skin is constantly directly exposed to air, solar radiation, environmental pollutants, or other mechanical and chemical factors, which can induce the generation of free radicals. Because the skin functions as a protective barrier between the body and its surroundings, the load of free radicals is higher in the skin than in other organs. Additionally, the normal aging process leads to the thinning of the skin layers, making the skin more susceptible to ultraviolet (UV) light and further increasing free radical formation. Exposure to high levels of UV light increases pigmentation and reduces skin elasticity, causing premature aging. Free radicals can also be produced in the skin during normal metabolism, independently of UV radiation and other environmental factors that may contribute to inflammation.

The beneficial health effects of astaxanthin on the skin have been investigated through dietary supplementation and by topical applications. Clinical studies demonstrated that astaxanthin supplementation and/or applying a cream with astaxanthin improved skin appearance, including skin tone, fine lines, and sallowness. The strongest improvements were observed in subjects using both the supplement and the topical products. Astaxanthin benefits for healthy skin at a glance are given in Table 4.

Table 4. Astaxanthin Benefits for Skin Health

Dietary supplementation and applications	• Reduces hyperpigmentation, wrinkle formation, and collagen breakdown; • Improves the skin elasticity and moisture content; • Prevents UV-induced skin damage; • Maintains a youthful appearance.
Dose	2, 4 or 6 mg/day
Time-to-effect	From 8-12 weeks
Gender	Females, males
Age	20-65
Markers of the effectiveness	• Patch test; • Visual inspection and evaluation of age spots, wrinkle image analysis; • Skin moisture content and transepidermal water loss; • Skin oil (sebum) content; • Questionnaires

5.3.1 Studies on Astaxanthin Benefits for Healthy Skin

Tominaga et al. (2012). "Cosmetic benefits of astaxanthin on human subjects." Acta Biochim Pol 59(1): 43-47. [38]

"Two human clinical studies were performed. One was an open-label non-controlled study involving 30 healthy female subjects for 8 weeks. Significant improvements were observed by combining 6 mg per day oral supplementation and 2 ml (78.9 muM solution) per day topical application of astaxanthin. Astaxanthin derived from the microalgae, *Haematococcus pluvialis* showed improvements in skin wrinkle (crow's feet at week-8), age spot size (cheek at week-8), elasticity (crow's feet at week-8), skin texture (cheek at week-4), moisture content of corneocyte layer (cheek in 10 dry skin subjects at week-8) and corneocyte condition (cheek at week-8). It may suggest that astaxanthin derived from *H. pluvialis* can improve skin condition in all layers such as corneocyte layer, epidermis, basal layer and dermis by combining oral supplementation and topical treatment. Another was a randomized double-blind placebo controlled study involving 36 healthy male subjects for 6 weeks. Crow's feet wrinkle and elasticity; and transepidermal water loss (TEWL) were improved after 6 mg of astaxanthin (the same as former study) daily supplementation. Moisture content and sebum oil level at the cheek zone showed strong tendencies for improvement. These results suggest that astaxanthin derived from *Haematococcus pluvialis* may improve the skin condition in not only in women but also in men."

Seiki et al. (2001). "Effects of astaxanthin from Haematococcus pluvialis on human skin." Fragrance Journal 2001(12): 98-103. [39]

"Astaxanthin is a natural color carotenoid found in salmon, salmon eggs, krill, and crab. Therefore, astaxanthin has been contained in the human diet for a long time. Astaxanthin from krill has been used for cosmetics to suppress post-UVB hyperpigmentation in human skin and food color additives. Recently, astaxanthin from Haematococcus pluvialis is available using new fermentation technology of *Haematococcus pluvialis* and it is used for dietary supplements, food color additives and cosmetics. Effects of astaxanthin from *Haematococcus pluvialis* on human subjects were tested. No serious adverse effects were observed by patch testing and sequencing applied test on human skin. In a pilot study, the skin repeated application test of cream containing astaxanthin on human skin showed the visual wrinkle reduction. The present paper described about patch testing, skin repeated application test, and a pilot study evaluating the wrinkle reduction effect on human skin."

Yoon et al. (2014). "Supplementating with dietary astaxanthin combined with collagen hydrolysate improves facial elasticity and decreases matrix metalloproteinase-1 and -12 expression: a comparative study with placebo." J Med Food 17(7): 810-816. [40]

"Photoaging accounts for most age-related changes in skin appearance. It has been suggested that both astaxanthin, a potent antioxidant, and collagen hydrolysate can be used as antiaging modalities in photoaged skin. However, there is no clinical study using astaxanthin combined with collagen hydrolysate. We investigated the effects of using a combination of dietary astaxanthin and collagen hydrolysate supplementation on moderately photoaged skin in humans. A total of 44 healthy subjects were recruited and treated with astaxanthin (2 mg/day) combined with collagen hydrolysate (3 g/day) or placebos, which were identical in appearance and taste to the active supplementation for 12 weeks. The elasticity and hydration properties of facial skin were evaluated using noninvasive objective devices. In addition, we also evaluated the expression of procollagen type I, fibrillin-1, matrix metalloproteinase-1 (MMP-1) and -12, and ultraviolet (UV)-induced DNA damage in artificially UV-irradiated buttock skin before and after treatment. The supplement group showed significant improvements in skin elasticity and transepidermal water loss in photoaged facial skin after 12 weeks compared with the placebo group. In the supplement group, expression of procollagen type I mRNA increased and expression of MMP-1 and -12 mRNA decreased compared with those in the placebo group. In contrast, there was no significant difference in UV-induced DNA damage between groups. These results demonstrate that dietary astaxanthin combined with collagen hydrolysate can improve elasticity and barrier integrity in photoaged human facial skin, and such treatment is well tolerated."

5.3.2 Supporting Studies on Astaxanthin and Skin Health

Iwabayashi et al. (2009). "Efficacy and safety of eight-week treatment with astaxanthin in individuals screened for increased oxidative stress burden." Anti-Aging Med 6(4): 15-21. [30]

The study was an open-label noncontrolled study in subjects with increased oxidative stress. Additional findings associated with skin health were observed: astaxanthin improved the physical symptoms of "cold skin" and "skin problems" after four and eight weeks respectively, as measured by an Anti-Aging QOL Common Questionnaire.

Phetcharat et al. (2015). "The effectiveness of a standardized rose hip powder, containing seeds and shells of Rosa canina, on cell longevity, skin wrinkles, moisture, and elasticity." Clin Interv Aging 10: 1849-1856. [41]

This study evaluated the effects of a rose hip powder made from seeds and shells on thirty-four healthy subjects, aged 35-65 years. Astaxanthin (dietary supplementation, 4 mg) was used as a positive control. Both treatments improved aging-induced skin conditions. Astaxanthin had a better effect on skin moisture.

5.4 Supports Healthy Aging

Aging is commonly defined as the accumulation of oxidative damage in cells and tissues with advancing age. Young cells are protected from free radicals by balanced activity of the mitochondria, efficient antioxidant and DNA repair systems, and active protein degradation machinery. Aging, on the other hand, is accompanied by mitochondrial dysfunction leading to increased free radical production, which in turn leads to an overloading of the defense systems and oxidative damage of cellular components [42]. That is why our body accumulates oxidative damage as we age, and we become more susceptible to certain health conditions. Characteristic aging symptoms associated with oxidative damage can be defined as:

- Age-related oxidation of blood lipids;
- Age-related cognitive decline, including mental awareness, information handling, and memory;
- Age-related granular pigment accumulation in retinal vessels, development of vascular lesions in the retinas;
- Age-related skin damage.

Natural astaxanthin may slow down or delay aging through reduced oxidative damage. Astaxanthin benefits for healthy aging at a glance are given in Table 5.

Table 5. Astaxanthin Benefits for Healthy Aging	
Dietary supplementation	• Delays aging through reduced oxidative damage of blood lipids; • Delays aging through reduced oxidative damage of skin; • Improves cognitive function in the healthy seniors; • Delays age-related vision degeneration by reducing free radicals in the aqueous humor and improving blood flow in capillaries in the eye.
Dose	2, 4, 6, 8 or 12 mg /day
Time-to-effect	From 4 to 48 weeks
Gender	Females, males
Age	45-70
Markers of the effectiveness	• Blood cell count and basic metabolic panel, including fatty acids, triglyceride, serum total cholesterol, LDL-cholesterol, HDL-cholesterol; • Oxidative stress biomarkers, such as malondialdehyde, isoprostane; • Bi-product of lipid peroxidation, such as phospholipid hydroperoxides and thiobarbituric acid reactive substances; • Vascular endothelial growth factor levels; • Superoxide scavenging activity, levels of hydrogen peroxide, and total hydroperoxides; • Cognitive tests.

5.4.1 Substation Studies Focused on Astaxanthin Benefits for Anti-Aging

Kim et al. (2004). "The Effects of Astaxanthin Supplements on Lipid Peroxidation and Antioxidant Status in Postmenopausal Women." Nutritional Sciences 7(1): 41-46. [35]

"In postmenopausal women, the incidence of cardiovascular disease(CVD) is common and there is growing evidences that astaxanthin has a strong antioxidant capacity and plays a beneficial role in the prevention of CVD. However, current data are not sufficient to determine the effect of astaxanthin on improving lipid profiles and antioxidant capacity in human. In this study, 15 healthy postmenopausal women were divided into 3 groups and given astaxanthin supplements of 0, 2 or 8mg/day for 8 weeks. Blood samples were taken before and after 4 and 8 weeks of astaxanthin supplementation for analysis of serum total choelsterol, LDL-cholesterol, HDL-cholesterol, triglyceride, plasma TBARS, total antioxidant status (TAS) and urinary 8-isoprostanes. HDL-cholesterol levels in 2mg and 8mg group increased significantly after 8 weeks from 50.6±5.8 to 60.4±7.1mg/dℓ, 44.4±10.7 to 49.4±2.7mg/dℓ respectively ($p<0.05$). In the 2mg group, triglyceride decreased significantly from 171.6±67.4 mg/dℓ to 145.8±5.1mg/dℓ ($p<0.05$). Plasma TBARS level in the 2mg group decreased from1.42± 0.18nM/mg to 1.13±0.18nM/mg after 8 weeks ($p<0.05$). In the 8mg group, TBARS level decreased significantly from 1.62±0.14nM/mg to 1.13±0.12nM/mg after 8 weeks ($p<0.05$). TAS, as an indicator of lipid peroxidation, increased significantly from 0.85±0.42mM/ℓ to 1.90±0.58mM/ℓ after 8 weeks in the 8mg group ($p<0.05$). Urinary 8-isoprostanes excretion did not decrease significantly with astaxanthin supplementation. In conclusion, it would be helpful for postmenopausal women with common cardiovascular disease to supplement with astaxanthin as an antioxidant. "

Nakagawa et al. (2011). "Antioxidant effect of astaxanthin on phospholipid peroxidation in human erythrocytes." Br J Nutr 105(11): 1563-1571. [36]

"Phospholipid hydroperoxides (PLOOH) accumulate abnormally in the erythrocytes of dementia patients, and dietary xanthophylls (polar carotenoids such as astaxanthin) are hypothesised to prevent the accumulation. In the present study, we conducted a randomised, double-blind, placebo-controlled human trial to assess the efficacy of 12-week astaxanthin supplementation (6 or 12 mg/d) on both astaxanthin and PLOOH levels in the erythrocytes of thirty middle-aged and senior subjects. After 12 weeks of treatment, erythrocyte astaxanthin concentrations were higher in both the 6 and 12 mg astaxanthin groups than in the placebo group. In contrast, erythrocyte PLOOH concentrations were lower in the astaxanthin groups than in the placebo group. In the plasma, somewhat lower PLOOH levels were found after astaxanthin treatment. These results suggest that astaxanthin supplementation results in improved erythrocyte antioxidant status and decreased PLOOH levels, which may contribute to the prevention of dementia."

Katagiri et al. (2012). "Effects of astaxanthin-rich *Haematococcus pluvialis* extract on cognitive function: a randomised, double-blind, placebo-controlled study." Journal of Clinical Biochemistry and Nutrition 51(2): 102-107. [43]

"In this study we tried to confirm the effect of an astaxanthin-rich Haematococcus pluvialis extract on cognitive function in 96 subjects by a randomised double-blind placebo-controlled study. Healthy middle-aged and elderly subjects who complained of age-related forgetfulness were recruited. Ninety-six subjects were selected from the initial screen, and ingested a capsule containing astaxanthin-rich Haematococcus pluvialis extract, or a placebo capsule for 12 weeks. Somatometry, haematology, urine screens, and CogHealth and Groton Maze Learning Test were performed before and after every 4 weeks of administration. Changes in cognitive performance and the safety of astaxanthin-rich *Haematococcus pluvialis* extract administration were evaluated. CogHealth battery scores improved in the high-dosage group (12 mg astaxanthin/day) after 12 weeks. Groton Maze Learning Test scores improved earlier in the low-dosage (6 mg astaxanthin/day) and high-dosage groups than in the placebo group. The sample size, however, was small to show a significant difference in cognitive function between the astaxanthin-rich Haematococcus pluvialis extract and placebo groups. No adverse effect on the subjects was observed throughout this study. In conclusion, the results suggested that astaxanthin-rich *Haematococcus pluvialis* extract improves cognitive function in the healthy aged individuals."

Hashimoto et al. (2016). "The effect of astaxanthin on vascular endothelial growth factor (VEGF) levels and peroxidation reactions in the aqueous humor." J Clin Biochem Nutr 59(1): 10-15. [44]

"We explored the effect of astaxanthin on vascular endothelial growth factor in the aqueous humor, by measuring vascular endothelial growth factor levels and oxidation-related parameters, including O2 (*-) scavenging activity, H2O2 level, and total hydroperoxide level in the aqueous humor, obtained from 35 patients before and after astaxanthin administration. We evaluated the relationship between vascular endothelial growth factor and the oxidation-related parameters as well as the patient's diabetic status, age, and sex. Vascular endothelial growth factor levels did not change significantly but O2 (*-) scavenging activity and total hydroperoxide level significantly ($p<0.05$) increased and decreased, respectively. Both pre- and post- astaxanthin intake, vascular endothelial growth factor and total hydroperoxide levels were positively correlated (Pearson: $r = 0.42$, $p<0.05$; $r = 0.55$, $p<0.01$, respectively). Analysis of vascular endothelial growth factor levels and O2 (*-) scavenging activities gave a negative correlation but only pre-astaxanthin intake ($r = -0.37$, $p<0.05$). Differences in levels pre- and post-astaxanthin only showed association between vascular endothelial growth factor and total hydroperoxide ($r = 0.49$, $p<0.01$) analyzed by multiple linear regression. Using multivariate analysis, pre-astaxanthin vascular endothelial growth factor level was associated with two factors of total hydroperoxide and O2 (*-) scavenging activity ($r = 0.49$, $p<0.05$), and post-astaxanthin vascular endothelial growth factor level with two factors of total hydroperoxide and sex ($r = 0.60$, $p<0.01$). Astaxanthin intake may have affected vascular endothelial growth factor level through its antioxidant effects by increasing O2 (*-) scavenging activity and suppressing peroxide production."

Hashimoto et al. (2013). "Effects of astaxanthin on antioxidation in human aqueous humor." J Clin Biochem Nutr 53(1): 1-7. [29]

"We evaluated the antioxidative effects of astaxanthin through the changes in superoxide scavenging activity, levels of hydrogen peroxide and total hydroperoxides in human aqueous humor. The study subjects were 35 patients who underwent bilateral cataract surgery on one side before and the other side after intake of astaxanthin (6 mg/day for 2 weeks). Their aqueous humor was taken during the surgery and subjected to measurements of the three parameters. After astaxanthin intake, the superoxide scavenging activity was significantly ($p<0.05$) elevated, while the level of total hydroperoxides was significantly ($p<0.05$) lowered. There was a significant negative correlation between the superoxide scavenging activity and the level of total hydroperoxides ($r = -0.485$, $p<0.01$), but no correlations between the hydrogen peroxide level and the other two parameters. Astaxanthin intake clearly enhanced the superoxide scavenging activity and suppressed the total hydroperoxides production in human aqueous humor, indicating the possibility that astaxanthin has suppressive effects on various oxidative stress-related diseases."

Saito et al. (2012). "Astaxanthin increases choroidal blood flow velocity." Graefes Arch Clin Exp Ophthalmol 250(2): 239-245. [37]

"PURPOSE: Previous studies have reported that astaxanthin (AXT) has antioxidative and anti-inflammatory effects in addition to its ability to shorten blood transit times. As laser speckle flowgraphy (LSFG) can noninvasively visualize the hemodynamics of the choroidal circulation, we used the technique to evaluate whether continuous ingestion of 12 mg of AXT per day could increase quantitative blood flow velocity. METHODS: In this randomized, double-blind, placebo-controlled study, we examined 20 healthy volunteers who ingested 12 mg AXT or placebo capsules over a 4-week period. LSFG was measured in the right eyes of all subjects at pre-ingestion, and at 2 and 4 weeks after the treatment of AXT. LSFG values were used to calculate the square blur rate (SBR), which is a quantitative index of relative blood flow velocity. RESULTS: A significant increase of the macular SBR was seen 4 weeks after AXT ingestion when compared to the pre-ingestion values (Wilcoxon signed-rank test, $P = 0.018$). In contrast, no statistical difference in the macular SBR was detected in the placebo group (Friedman test, $P = 0.598$). No subjective or objective adverse events were found after the 12-mg AXT ingestion. CONCLUSIONS: Results suggest that administration of AXT over a 4-week period can elevate the choroidal blood flow velocity without any adverse effects."

5.4.2 Supporting Studies on Astaxanthin and Healthy Aging

Yoon et al. (2014). "Supplementating with dietary astaxanthin combined with collagen hydrolysate improves facial elasticity and decreases matrix metalloproteinase-1 and -12 expression: a comparative study with placebo." J Med Food 17(7): 810-816. [40]

The study focused on astaxanthin and collagen effects on the aging skin. An abstract is given under Healthy Skin.

Miyazawa et al. (2011). "Erythrocytes carotenoids after astaxanthin supplementation in middle-aged and senior Japanese subjects." J Oleo Sci 60(10): 495-499. [45]

The study accessed the effect of astaxanthin on the carotenoid compositions of erythrocytes in middle-aged and senior subjects.

Miyazawa et al. (2011). "Plasma carotenoid concentrations before and after supplementation with astaxanthin in middle-aged and senior subjects." Biosci Biotechnol Biochem 75(9): 1856-1858. [46]

The study examined the bioavailability of astaxanthin in middle-aged and senior subjects.

5.5 Supports the Body's Recovery from Heavy Exercise

Natural astaxanthin has a strong potential in sports nutrition. As a bioavailable antioxidant, astaxanthin is transported throughout the body to organs and muscle tissues, combating excessive free radical production by athletes.

Heavy exercise is energy dependent. When the muscles burn calories by oxidation, free radicals are formed as a by-product [47]. Free radicals can damage the muscles and reduce their ability to contract [48]. It has been shown that athletes have increased free radical levels in the blood, and lower levels of antioxidants [1]. One of the reasons that heavy exercise has negative effects is that free radical formation exceeds the capacity of antioxidant defense in the body. Another reason is that blood flow is closed off to different tissues, organs, and parts of the muscles during exercise. This causes a lack of oxygen (ischemia). When oxygen returns to these areas (reperfusion), various free radical compounds are formed [49]. Oxidative stress is implicated in the development of muscle pain, weakness, and fatigue. Natural astaxanthin improves muscle function by reducing free radical damage. The benefits of Astaxanthin for the body's recovery from heavy exercise at a glance are given in Table 6.

Table 6. Astaxanthin Benefits for Body's Recovery from Heavy Exercise

Dietary supplementation	• Improves muscle endurance and strength; • Reduces muscle fatigue; • Protects against exercise-induced free radical production; • Inhibits the formation of lactic acid.
Dose	4 - 6 mg /day
Time-to-effect	4 to 24 weeks
Gender	Males (clinical studies with women in regards to the body in recovery from heavy exercise are still lacking)
Age	17-39
Markers of the effectiveness	• Endurance testing, such as maximal oxygen uptake (VO2) test, cycling time trial. • Whole blood test, including cholesterol (LDL, HDL), triglycerides, lactic acid, glucose. • Muscle enzymes, such as aspartate aminotransferase, creatine, kinase. • Biomarkers of oxidative stress, such as advanced oxidation protein products, redox balance, as well as the content of total -SH groups and thiobarbituric acid-reactive substances.

5.5.1 Studies Focused On Astaxanthin Benefits in the Body's Recovery from Heavy Exercise

Baralic et al. (2013). "Effect of astaxanthin supplementation on paraoxonase 1 activities and oxidative stress status in young soccer players." Phytother Res 27(10): 1536-1542. [50]

"The purpose of the study was to examine the effects of astaxanthin (Asx) on paraoxonase (PON1) activities and oxidative stress status in soccer players. Forty soccer players were randomly assigned in a double-blind fashion to Asx and placebo (P) group. Blood samples were obtained before, 45 and 90 days after supplementation. PON1 activity was assessed by using two substrates: paraoxon and diazoxon. The oxidative stress biomarkers were also examined: total sulphydryl group content (-SH groups), thiobarbituric acid-reactive substances (TBARS), advanced oxidation protein products and redox balance. The significant interaction effect of supplementation and training ($p < 0.05$) on PON1 activity toward paraoxon was observed. The PON1 activity toward diazoxon increased in Asx group after 90 days ($p < 0.01$), while there was no significant difference in P group. SH groups content rose from pre- to post-supplementation period only in Asx group (supplementation and training, $p < 0.05$; training, $p < 0.01$). TBARS levels decreased after 45 days and increased after 90 days of regular soccer training in both groups (training, $p < 0.001$). Redox balance decreased significantly in response to the regular training, regardless of treatment group (training, $p < 0.001$). Asx supplementation might increase total SH groups content and improve PON1 activity through protection of free thiol groups against oxidative modification."

Baralic et al. (2015). "Effect of Astaxanthin Supplementation on Salivary IgA, Oxidative Stress, and Inflammation in Young Soccer Players." Evid Based Complement Alternat Med 2015: 783761. [27]

"The physiologic stress induced by physical activity is reflected in immune system perturbations, oxidative stress, muscle injury, and inflammation. We investigated the effect of astaxanthin (Asx) supplementation on salivary IgA (sIgA) and oxidative stress status in plasma, along with changes in biochemical parameters and total/differential white cell counts. Forty trained male soccer players were randomly assigned to Asx and placebo groups. Asx group was supplemented with 4 mg of Asx. Saliva and blood samples were collected at the baseline and after 90 days of supplementation in preexercise conditions. We observed a rise of sIgA levels at rest after 90 days of Asx supplementation, which was accompanied with a decrease in prooxidant-antioxidant balance. The plasma muscle enzymes levels were reduced significantly by Asx supplementation and by regular training. The increase in neutrophil count and hs-CRP level was found only in placebo group, indicating a significant blunting of the systemic inflammatory response in the subjects taking Asx. This study indicates that Asx supplementation improves sIgA response and attenuates muscle damage, thus preventing inflammation induced by rigorous physical training. Our findings also point that Asx could show significant physiologic modulation in individuals with mucosal immunity impairment or under conditions of increased oxidative stress and inflammation."

Djordjevic et al. (2012). "Effect of astaxanthin supplementation on muscle damage and oxidative stress markers in elite young soccer players." J Sports Med Phys Fitness 52(4): 382-392. [51]

"AIM: The purpose of the current study was to examine the effect of Astaxanthin (Asx) supplementation on muscle enzymes as indirect markers of muscle damage, oxidative stress markers and antioxidant response in elite young soccer players. METHODS: Thirty-two male elite soccer players were randomly assigned in a double-blind fashion to Asx and placebo (P) group. After the 90 days of supplementation, the athletes performed a 2 hour acute exercise bout. Blood samples were obtained before and after 90 days of supplementation and after the exercise at the end of observational period for analysis of thiobarbituric acid-reacting substances (TBARS), advanced oxidation protein products (AOPP), superoxide anion ($O2^*$), total antioxidative status (TAS), sulphydril groups (SH), superoxide-dismutase (SOD), serum creatine kinase (CK) and aspartate aminotransferase (AST). RESULTS: TBARS and AOPP levels did not change throughout the study. Regular training significantly increased $O2^*$ levels (main training effect, $P<0.01$). $O2^*$ concentrations increased after the soccer exercise (main exercise effect, $P<0.01$), but these changes reached statistical significance only in the P group (exercise x supplementation effect, $P<0.05$). TAS levels decreased significantly post- exercise only in P group ($P<0.01$). Both Asx and P groups experienced increase in total SH groups content (by 21% and 9%, respectively) and supplementation effect was marginally significant ($P=0.08$).

Basal SOD activity significantly decreased both in P and in Asx group by the end of the study (main training effect, P<0.01). All participants showed a significant decrease in basal CK and AST activities after 90 days (main training effect, P<0.01 and P<0.001, respectively). CK and AST activities in serum significantly increased as result of soccer exercise (main exercise effect, P<0.001 and P<0.01, respectively). Postexercise CK and AST levels were significantly lower in Asx group compared to P group (P<0.05) CONCLUSION: The results of the present study suggest that soccer training and soccer exercise are associated with excessive production of free radicals and oxidative stress, which might diminish antioxidant system efficiency. Supplementation with Asx could prevent exercise induced free radical production and depletion of non-enzymatic antioxidant defense in young soccer players."

Earnest et al. (2011). "Effect of astaxanthin on cycling time trial performance." Int J Sports Med 32(11): 882-888. [52]

"We examined the effect of Astaxanthin (AST) on substrate metabolism and cycling time trial (TT) performance by randomly assigning 21 competitive cyclists to 28 d of encapsulated AST (4 mg/d) or placebo (PLA) supplementation. Testing included a VO2max test and on a separate day a 2 h constant intensity pre-exhaustion ride, after a 10 h fast, at 5% below VO2max stimulated onset of 4 mmol/L lactic acid followed 5 min later by a 20 km TT. Analysis included ANOVA and post-hoc testing. Data are Mean (SD) and (95% CI) when expressed as change (pre vs. post). Fourteen participants successfully completed the trial. Overall, we observed significant improvements in 20 km TT performance in the AST group (n=7; -121 s; 95% CI, -185, -53), but not the PLA (n=7; -19 s; 95% CI, -84, 45). The AST group was significantly different vs. PLA (P<0.05). The AST group significantly increased power output (20 W; 95% CI, 1, 38), while the PLA group did not (1.6 W; 95% CI, -17, 20). The mechanism of action for these improvements remains unclear, as we observed no treatment effects for carbohydrate and fat oxidation, or blood indices indicative of fuel mobilization. While AST significantly improved TT performance the mechanism of action explaining this effect remains obscure."

Malmsten et al. (2009). "Dietary supplement with astaxanthin-rich algal meal improves strenght endurance - A double blind placebo controlled study on male students. ." Carotenoid Science 13: 20-22. [53]

"The present study was designed to investigate the effect of dietary supplementation with astaxanthin on physical performance. Forty healthy paramedic students were recruited for this test in a double blind placebo controlled study. In this study, we used algal meal (AstaREAL® biomass) as astaxanthin supplementation. Twenty of the subjects received capsules filled with algal meal to provide 4 mg astaxanthin per capsule, whereas the other twenty received placebo capsules for six months. The physical parameters monitored were fitness, strength/endurance and strength/explosivity by standardized exercises. Before starting the dietary supplementation, base values for each of the subjects were obtained. At the end of the six month period of dietary supplementation, the average number of knee bendings (squats) increased by 27.05 (from 49.32 to 76.37) for subjects having received astaxanthin and by 9.0 (from 46.06 to 55.06) for the placebo subjects. Hence, the increase in the astaxanthin supplemented group was three times higher than that of the placebo group (P=0.047). None of the other parameters monitored differed significantly between the groups at the end of the study period. Based on this findings, it suggested that supplementation of astaxanthin is effective for the improvement of strength endurance that may lead to sports performance."

5.5.2 Supporting Study on Astaxanthin and Body Recovery From Heavy Exercise

Sawaki et al. (2002). "Sports Performance Benefits from Taking Natural Astaxanthin: Characterized by Visual Acuity and Muscular Fatigue Improvement in Humans " Journal of Traditional Medicines 19(5). [54]

The study reported improvement of visual acuity and muscle fatigue after dietary supplementation with astaxanthin.

6 Combinatorial Applications of Astaxanthin

Combined usage of natural ingredients may provide synergistic/additive effects for neutralizing free radicals. This might be achieved indirectly by combining astaxanthin with lipophilic ingredients (such as fish oil, Perilla seed oil, or sunflower-based phospholipids) for increased bioavailability and absorption. The alternative, direct approach would be a combination of ingredients with synergistic actions. This is a relatively new and evolving research field even though the idea of an antioxidant network was proposed some years ago [55]. Scientists suggested a hypothesis that the components in the antioxidant network work as a team and different antioxidants also work in different parts of the cell, depending on whether they are water or lipid soluble. For example, water-based vitamin C and glutathione protect the cell nucleus. Astaxanthin is lipid soluble, and has a special affinity for cell membranes.

Complex dietary supplements containing astaxanthin increased the total antioxidant capacity of plasma, reduced lipid peroxidation, and improved lipid profiles in large clinical studies [56-58]. High doses of astaxanthin in combination with EPA and vitamin E have been successfully tested as a medical food for the management of elevated triacylglycerols [57]. A catalog of ingredients used in combinatory applications with astaxanthin in clinical studies is given in Table 7.

Table 7. Ingredients Used in Combinatory Applications with Astaxanthin (Moderate or High Dose*) in Clinical Studies [56-61]

Lutein, zeaxanthin, lycopene		Other naturally occurring carotenoids.
Fish oil **Docosahexaenoic acid (DHA)** **Eicosapentaenoic acid (EPA)**		Omega-3 fatty acid that is a primary structural component of the human brain, cerebral cortex, skin, sperm, testicles, and retina.
Herbal extracts	Chrysanthemin (Cyanidin-3-Glucoside)	Polyphenols, natural colorant found in bilberries and other fruits and flowers.
	Hawthorn (extract from *Crataegus mongyna*)	Extract containing a variety of bioflavonoids.
	Vitexin	C-glycosylated flavone present in several herbs.
	Selenomethionine	A naturally occurring amino acid, L-selenomethionine enantiomer is the main form of selenium found in Brazil nuts and cereal grains.
Vitamin C, vitamin E, vitamin D, Ubiquinone (Q10)		Vitamins
Zinc, copper, selenium Minerals		Minerals

**The cataloged combinatory ingredients have been used with a moderate dose, 4 mg/day, or high dose, 12 and 15 mg/day. of astaxanthin.*

7 Conclusion

This document is a synopsis of human clinical research on natural astaxanthin derived from *Haematococcus pluvialis*. Natural astaxanthin has been demonstrated as a safe nutrient with no side effects. The health benefits of natural astaxanthin have been linked to its mode of action as a strong antioxidant. Current data indicate that astaxanthin is a valuable functional ingredient with applications for skin health, anti-aging, muscle endurance/recovery, and cardiovascular health.

Dietary supplements and functional foods are a good way to increase the daily intake of astaxanthin, which otherwise may be consumed in less-than-recommended amounts. It is a promising strategy to maintain good health and well-being and offers exciting opportunities for the nutraceutical industry.

8 Bibliography

1. Balakrishnan S, Anuradha C (1998) Exercise, depletion of antioxidants and antioxidant manipulation. Cell Biochem Funct 16:269-75.
2. Niyogi KK, Bjorkman O, Grossman AR (1997) The roles of specific xanthophylls in photoprotection. Proc. Natl. Acad. Sci. U.S.A 94:14162-67.
3. Nishida Y, Yamashita E, Miki W (2007) Quenching Activities of Common Hydrophilic and Lipophilic Antioxidants against Singlet Oxygen Using Chemiluminescence Detection System. Carotenoid Science 11:16-20.
4. Beutner S, Bloedorn B, Frixel S, Hernández Blanco I, et al. (2001) Quantitative assessment of antioxidant properties of natural colorants and phytochemicals: carotenoids, flavonoids, phenols and indigoids. The role of β-carotene in antioxidant functions. Journal of the Science of Food and Agriculture 81:559-68.
5. Capelli B, Bagchi D, Cysewski G (2013) Synthetic astaxanthin is significantly inferior to algal-based astaxanthin as an antioxidant and may not be suitable as a human nutraceutical supplement. Nutrafoods 12:145-52.
6. FDA (1999) Cyanotech Premarket Notification for New Dietary Ingredient: Haematococcus pluvialis algae.
7. FDA (2000) Technical Report (Aquaresearch Inc.) Haematococcus Pluvialis and Astaxanthin Safety For Human Consumption.
8. Spiller GA, Dewell A (2003) Safety of an astaxanthin-rich Haematococcus pluvialis algal extract: a randomized clinical trial. J. Med. Food 6:51-56.
9. Stewart JS, Lignell A, Pettersson A, Elfving E, et al. (2008) Safety assessment of astaxanthin-rich microalgae biomass: Acute and subchronic toxicity studies in rats. Food Chem Toxicol 46:3030-6.
10. Okada Y, Ishikura M, Maoka T (2009) Bioavailability of astaxanthin in Haematococcus algal extract: the effects of timing of diet and smoking habits. Biosci Biotechnol Biochem 73:1928-32.
11. Fuji Chemical Industry Co. L (2009) Notification of GRAS Determination for Haematococus pluvialis extract characterized by component astaxanthin esters (of common edible fatty acids).
12. Fuji Chemical Industry Co. L (2004) New Dietary Ingredient Notification for Astaxanthin Extracted from Haematococcus Algae
13. EFSA (2014) Scientific Opinion on the safety of astaxanthin-rich ingredients (AstaREAL A1010 and AstaREAL L10) as novel food ingredients.
14. Bjerkeng B, Hatlen B, Jobling M (2000) Astaxanthin and its metabolites idoxanthin and crustaxanthin in flesh, skin, and gonads of sexually immature and maturing Arctic charr (Salvelinus alpinus (L.)). Comp Biochem Physiol B Biochem Mol Biol 125:395-404.
15. Osterlie M, Bjerkeng B, Liaaen-Jensen S (2000) 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:
16. Odeberg JM, Lignell Å, Pettersson A, Høglund P (2003) Oral bioavailability of the antioxidant astaxanthin in humans is enhanced by incorportaion of lipid based formulations. European Journal of Pharmaceutical Sciences 19:299-304.
17. Coral-Hinostroza GN, Ytrestoyl T, Ruyter B, Bjerkeng B (2004) Plasma appearance of unesterified astaxanthin geometrical E/Z and optical R/S isomers in men given single doses of a mixture of optical 3 and 3'R/S isomers of astaxanthin fatty acyl diesters. Comp Biochem Physiol C Toxicol Pharmacol 139:99-110.
18. Rufer C, Moesenede J, Briviba K, Rechkemmer G, et al. (2008) Bioavailability of astaxanthin stereoisomers from wild (Oncorhynchus spp.) and aquacultured (Salmo salar) salmon in healthy men: a randomised, double-blind study. Br J Nutr 99:1048-54.
19. Moretti VM, Mentasti T, Bellagamba F, Luzzana U, et al. (2006) Determination of astaxanthin stereoisomers and colour attributes in flesh of rainbow trout (Oncorhynchus mykiss) as a tool to distinguish the dietary pigmentation source. Food Addit Contam 23:1056-63.
20. Bjerkeng B, Berge GM (2000) Apparent digestibility coefficients and accumulation of astaxanthin E/Z isomers in Atlantic salmon (Salmo salar L.) and Atlantic halibut (Hippoglossus hippoglossus L.). Comp Biochem Physiol B Biochem Mol Biol 127:423-32.
21. Zhou Q, Xu J, Yang S, Xue Y, et al. (2015) The Effect of Various Antioxidants on the Degradation of O/W Microemulsions Containing Esterified Astaxanthins from Haematococcus pluvialis. Journal of Oleo Science 64:515-25.
22. de Bruijn WJC, Weesepoel Y, Vincken J-P, Gruppen H (2016) Fatty acids attached to all-trans-astaxanthin alter its cis–trans equilibrium, and consequently its stability, upon light-accelerated autoxidation. Food Chemistry 194:1108-15.

23. Decker EA, Faustman C, Lopez-Bote CJ (2000) Antioxidants in Muscle Foods: Nutritional Strategies to Improve Quality. John Wiley & Sons.
24. Kim JH, Chang MJ, Choi HD, Youn YK, et al. (2011) Protective effects of Haematococcus astaxanthin on oxidative stress in healthy smokers. J Med Food 14:1469-75.
25. Choi HD, Kim JH, Chang MJ, Kyu-Youn Y, et al. (2011) Effects of astaxanthin on oxidative stress in overweight and obese adults. Phytother Res 25:1813-8.
26. Park JS, Chyun JH, Kim YK, Line LL, et al. (2010) Astaxanthin decreased oxidative stress and inflammation and enhaced immune response in humans. Nutr Metab (Lond) 7:18.
27. Baralic I, Andjelkovic M, Djordjevic B, Dikic N, et al. (2015) Effect of Astaxanthin Supplementation on Salivary IgA, Oxidative Stress, and Inflammation in Young Soccer Players. Evid Based Complement Alternat Med 2015:783761.
28. Choi HD, Youn YK, Shin WG (2011) Positive effects of astaxanthin on lipid profiles and oxidative stress in overweight subjects. Plant Foods Hum Nutr 66:363-9.
29. Hashimoto H, Arai K, Hayashi S, Okamoto H, et al. (2013) Effects of astaxanthin on antioxidation in human aqueous humor. J Clin Biochem Nutr 53:1-7.
30. Iwabayashi M, Fujioka N, Nomoto K, Miyazaki R, et al. (2009) Efficacy and safety of eight-week treatment with astaxanthin in individuals screened for increased oxidative stress burden. Anti-Aging Med 6:15-21.
31. Yamada TR, Ryo K.; Tai, Y; Tamaki, Y; Inoue, H; Mishima, K; Tsubota, K; Saito, I (2010) Evaluation of therapeutic effects of astaxanthin on impairments in salivary secretion. J Clin Biochem Nutr 47:130-7.
32. Yoshida H, Yanai H, Ito K, Tomono Y, et al. (2010) Administration of natural astaxanthin increases serum HDL-cholesterol and adiponectin in subjects with mild hyperlipidemia. Atherosclerosis 209:520-3.
33. Karppi J, Rissanen TH, Nyyssonen K, Kaikkonen J, et al. (2007) Effects of astaxanthin supplementation on lipid peroxidation. Int J Vitam Nutr Res 77:3-11.
34. Miyawaki H, Takahashi J, Tsukahara H, Takehara I (2008) Effects of Astaxanthin on Human Blood Rheology. Journal of Clinical Biochemistry and Nutrition 43:69-74.
35. Kim YK, Chyun JH (2004) The Effects of Astaxanthin Supplements on Lipid Peroxidation and Antioxidant Status in Postmenopausal Women. Nutritional Sciences 7:41-46.
36. Nakagawa K, Kiko T, Miyazawa T, Carpentero Burdeos G, et al. (2011) Antioxidant effect of astaxanthin on phospholipid peroxidation in human erythrocytes. Br J Nutr 105:1563-71.
37. Saito M, Yoshida K, Saito W, Fujiya A, et al. (2012) Astaxanthin increases choroidal blood flow velocity. Graefes Arch Clin Exp Ophthalmol 250:239-45.
38. Tominaga K, Hongo N, Karato M, Yamashita E (2012) Cosmetic benefits of astaxanthin on humans subjects. Acta Biochim Pol 59:43-7.
39. Seiki T, Sueki H, Kohni H, Suganuma K, et al. (2001) Effects of astaxanthin from Haematococcus pluvialis on human skin. Fragrance Journal 2001:98-103.
40. Yoon HS, Cho HH, Cho S, Lee SR, et al. (2014) Supplementating with dietary astaxanthin combined with collagen hydrolysate improves facial elasticity and decreases matrix metalloproteinase-1 and -12 expression: a comparative study with placebo. J Med Food 17:810-6.
41. Phetcharat L, Wongsuphasawat K, Winther K (2015) The effectiveness of a standardized rose hip powder, containing seeds and shells of Rosa canina, on cell longevity, skin wrinkles, moisture, and elasticity. Clin Interv Aging 10:1849-56.
42. Shigenaga MK, Hagen TM, Ames BN (1994) Oxidative damage and mitochondrial decay in aging. Proc Natl Acad Sci U S A 91:10771-8.
43. Katagiri M, Satoh A, Tsuji S, Shirasawa T (2012) Effects of astaxanthin-rich Haematococcus pluvialis extract on cognitive function: a randomised, double-blind, placebo-controlled study. Journal of Clinical Biochemistry and Nutrition 51:102-07.
44. Hashimoto H, Arai K, Hayashi S, Okamoto H, et al. (2016) The effect of astaxanthin on vascular endothelial growth factor (VEGF) levels and peroxidation reactions in the aqueous humor. J Clin Biochem Nutr 59:10-5.
45. Miyazawa T, Nakagawa K, Kimura F, Satoh A, et al. (2011) Erythrocytes carotenoids after astaxanthin supplementation in middle-aged and senior Japanese subjects. J Oleo Sci 60:495-9.
46. Miyazawa T, Nakagawa K, Kimura F, Satoh A, et al. (2011) Plasma carotenoid concentrations before and after supplementation with astaxanthin in middle-aged and senior subjects. Biosci Biotechnol Biochem 75:1856-8.
47. Turrens JF, Boveris A (1980) Generation of superoxide anion by the NADH dehydrogenase of bovine heart mitochondria. Biochem J 191:421-7.

48. Fulle S, Pietrangelo T, Bellomo R, Sagnella D, et al. (2004) The relationship between oxidative stress and the functional capacity of skeletal muscle. Basic Appl Myol 14:33-36.
49. Zweier JL, Flaherty JT, Weisfeldt ML (1987) Direct measurement of free radical generation following reperfusion of ischemic myocardium. Proc Natl Acad Sci U.S.A. 84:1404-7.
50. Baralic I, Djordjevic B, Dikic N, Kotur-Stevuljevic J, et al. (2013) Effect of astaxanthin supplementation on paraoxonase 1 activities and oxidative stress status in young soccer players. Phytother Res 27:1536-42.
51. Djordjevic B, Baralic I, Kotur-Stevuljevic J, Stefanovic A, et al. (2012) Effect of astaxanthin supplementation on muscle damage and oxidative stress markers in elite young soccer players. J Sports Med Phys Fitness 52:382-92.
52. Earnest CP, Lupo M, White KM, Church TS (2011) Effect of astaxanthin on cycling time trial performance. Int J Sports Med 32:882-8.
53. Malmsten C, Lignell Å (2009) Dietary supplement with astaxanthin-rich algal meal improves strenght endurance - A double-blind placebo-controlled study on male students. Carotenoid Science 13:20-22.
54. Sawaki K, Yoshigi H, Aoki K, Koikawa N, et al. (2002) Sports Performance Benefits from Taking Natural Astaxanthin: Characterized by Visual Acuity and Muscular Fatigue Improvement in Humans. Journal of Traditional Medicines 19:1-11.
55. Sies H, Stahl W, Sevanian A (2005) Nutritional, Dietary and Postprandial Oxidative Stress. The Journal of Nutrition 135:969-72.
56. Izzo R, de Simone G, Giudice R, Chinali M, et al. (2010) Effects of nutraceuticals on prevalence of metabolic syndrome and on calculated Framingham Risk Score in individuals with dyslipidemia. J Hypertens 28:1482-7.
57. Maki KC, Geohas JG, Dicklin MR, Huebner M, et al. (2015) Safety and lipid-altering efficacy of a new omega-3 fatty acid and antioxidant containing medical food in men and women with elevated triacylglycerols. Prostaglandins Leukot Essent Fatty Acids 99:41-6.
58. Balcerczyk A, Gajewska A, Macierzynska-Piotrowska E, Pawelczyk T, et al. (2014) Enhanced antioxidant capacity and anti-ageing biomarkers after diet micronutrient supplementation. Molecules 19:14794-808.
59. Kono K, Shimizu Y, Takahashi S, Matsuoka S, et al. (2014) Effect of Multiple Dietary Supplement Containing Lutein, Astaxanthin, Cyanidin-3-Glucoside, and DHA on Accommodative Ability. Current Medicinal Chemistry 14:114-25.
60. Parisi V, Tedeschi M, Gallinaro G, Varano M, et al. (2008) Carotenoids and antioxidants in age-related maculopathy italian study: multifocal electroretinogram modifications after 1 year. Ophthalmology 115:324-33 e2.
61. Piermarocchi S, Saviano S, Parisi V, Tedeschi M, et al. (2012) Carotenoids in Age-related Maculopathy Italian Study (CARMIS): two-year results of a randomized study. Eur J Ophthalmol 22:216-25.
62. Iwasaki T, Tahara A (2006) Effects of Astaxanthin on Eyestrain Induced by Accommodative Dysfunction. Journal of the Eye 23:826-34.
63. Nagaki Y, Hayasaja S, Yamada T, Hayasaka Y, et al. (2002) Effects of astaxanthiq on accommodation, critical flicker fusion, and pattern visual evoked potential in visual display terminal workers. Journal of Traditional Medicines 19:170-73.
64. Nakamura A, Isobe R, Otaka Y, Abenatsu Y, et al. (2004) Changes in visual function following peroral astaxanthin. Japanese Journal of Clinical Ophthalmology 58:1051-54.
65. Comhaire FH, El Garem Y, Mahmoud A, Eertmans F, et al. (2005) Combined conventional/antioxidant “Astaxanthin” treatment for male infertility: a double-blind, randomized trial. Asian J Androl 7:257-62.
66. Spiller GA, Dewell A, Chaves S, Rakidzich Z (2006) Effect of daily use of natural astaxanthin on symptoms associated with tennis elbow (lateral humeral epicondylitis). Cyanotech Rapport.

9 Appendix

Table 1. A comprehensive summary of clinical studies using natural astaxanthin from *Haematococcus pluvialis*.

NA - Data not available

First author	Year	Number of test subjects	Number of test treated subject	Number of control/placebo subjects	Gender	Supplementation	Treatment time, weeks	Daily dose, mg	Application	Reference
Nakagawa	2011	30	20	10	females, males	oral	12	6 and 12	Anti-Aging/Cardiovascular/Neurological	[36]
Hashimoto	2013	35	35	NA	males, females	oral	2	6	Anti-Aging/Eye health	[29]
Hashimoto	2016	35	35	35	females, males	oral	2	6	Anti-Aging/Eye health	[44]
Saito	2012	20	10	10	females, males	oral	4	12	Anti-Aging/Eye Health/Cardiovascular	[37]
Katagiri	2012	96	64	32	females, males	oral	12	6 and 12	Anti-Aging/Neurological	[43]
Miyazawa	2011	20	20	0	NA	oral	12	1 and 3	Bioavaibility/Aging	[45]
Miyazawa	2011	20	20	0	NA	oral	12	1 and 3	Bioavaibility/Aging	[46]
Odeberg	2003	32	32	0	males	oral	single dose	40	Bioavilability	[16]
Spiller	2003	35	19	16	females, males	oral	8	6	Bioavilability	[8]
Okada	2009	20	20	0	females, males	oral	single dose	48	Bioavilability	[10]
Karppi	2007	40	20	20	males	oral	12	8	Cardiovascular	[33]
Kim	2004	15	10	5	females	oral	8	2 and 8	Cardiovascular	[35]
Miyawaki	2008	20	10	10	males	oral	1,5	6	Cardiovascular	[34]
Yoshida	2010	61	46	15	females, males	oral	12	6; 12 and 18	Cardiovascular	[32]
Iwabayashi	2009	21	21	0	females	oral	8	12	Cardiovascular/Oxidative stress/Skin	[30]
Iwasaki	2006	10	5	5	females, males	oral	2	6	Eye health	[62]
Nagaki	2002	39	13	26	females, males	oral	4	5	Eye health	[63]
Nakamura	2004	49	30	10	females, males	oral	4	2; 4 and 12	Eye Health	[64]
Comhaire	2005	30	11	19	males	oral	12	16	Fertility	[65]
Sawaki	2002	18	9	9	males	oral	4	6	Muscle performance/Eye health	[54]
Baralic	2013	40	20	20	males	oral	12	NA	Muscle performance	[50]
Djordjevic	2012	32	18	14	males	oral	12	4	Muscle performance	[51]
Earnest	2011	14	7	7	males	oral	4	4	Muscle performance	[52]
Malmsten	2008	40	20	20	males	oral	24	4	Muscle performance	[53]
Baralic	2015	40	21	19	males	oral	12	4	Muscle performance/Oxidative stress	[27]
Choi	2011	33	23	10	females, males	oral	3	5 and 20	Oxidative stress	[25]
Choi	2011	27	14	13	females, males	oral	12	20	Oxidative stress	[28]
Kim	2011	78	39	39	females, males	oral	3	5; 20 and 40	Oxidative stress	[24]
Park	2010	42	28	14	females	oral	8	2 and 8	Oxidative stress/Immunity	[26]
Yamada	2010	12	6	6	NA	oral	2	12	Oxidative stress/Immunity	[31]
Seiki	2001	56	45/11	0	females, males	topical	24	NA	Skin	[39]
Tominaga	2012	66	66	0	females, males	oral, topical	8	6	Skin	[38]
Yoon	2014	44	22	22	females	oral	12	2	Skin	[40]
Phetcharat	2015	34	6	28	females, males	oral	8	4	Skin/Anti-aging	[41]
Spiller	2006	33	21	12	females, males	oral	8	4	Tennis Elbow	[66]

www.algalif.com | sales@algalif.com