Natural Astaxanthin:
Human Clinical Studies Overview

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Natural Astaxanthin: Human Clinical Studies Overview

In clinical studies, astaxanthin has been mainly used as a single component (82%), although studies with astaxanthin in combination with other nutrients are also available (18%) (Fig.2 B). A thorough examination of astaxanthin sources used in these studies revealed that natural astaxanthin was largely obtained from *Haematococcus pluvialis*. This provides evidence that astaxanthin from algal sources is the best documented when it comes to health benefits.

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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.

Astaxanthin as an Antioxidant

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

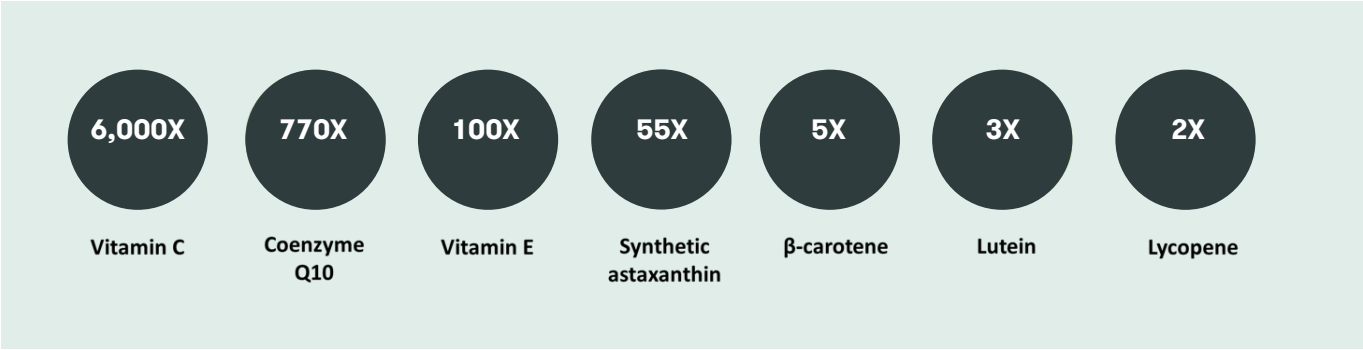
Natural astaxanthin is a powerful antioxidant and neutralizes free radicals. The health benefits of natural astaxanthin can be explained by understanding how an antioxidant works.

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 very 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 bi-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, unhealthy diet, excessive sunbathing, heavy exercise, smoking, etc.

The formation of the potential harmful ROS bi-products often involves chain reactions which increase in extent if they are not stopped. It is estimated that each cell in the body forms more than 20 trillion of ROS per day through normal metabolism, and each cell in the body 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 defence mechanism can counteract. This damages cellular structures, lipids, proteins and genetic material (DNA).

A. Natural astaxanthin is more powerful than other antioxidants in trapping energy from free radicals, such as singlet oxygen ($^1O_2$) [3, 5].



B. Structural formulas of astaxanthin.

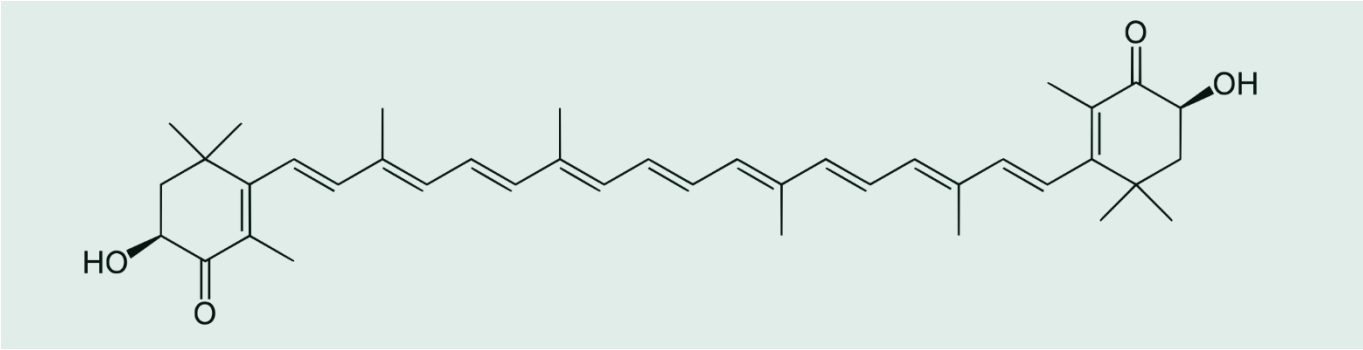


Figure 1.
A. Natural astaxanthin is more powerful than other antioxidants in trapping energy from free radicals, such as singlet oxygen ($^1O_2$) [3, 4].
B. Astaxanthin consists of two terminal rings joined by a polyene chain.

Natural astaxanthin is considered as “super antioxidant” and possesses one of the strongest known antioxidant effects.

• 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 signalling pathways. In many cases, it leads to pro-inflammatory processes.
• Protein oxidation can cause fragmentation at amino acid residues, formation of protein-protein cross-linkages, and oxidation of the protein backbone which ultimately leads to loss of function. Damaged proteins affect intracellular signalling pathways and are contributing factors to different disorders.
• DNA oxidation causes alterations in DNA bases. If left unrepaired, the modifications of DNA bases lead to genetic defects, 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 body accumulates 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. These antioxidants delay or inhibit cellular damage mainly through their free radical scavenging property. Dietary intake is a very important source of antioxidants.

Natural astaxanthin is considered as “super antioxidant” and possesses one of the strongest known antioxidant effects. Astaxanthin consists of two terminal rings joined by a polyene chain (Fig. 1 B). 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 6,000 times more capable than vitamin C, 100 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 A). Astaxanthin has also the ability to 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].

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].

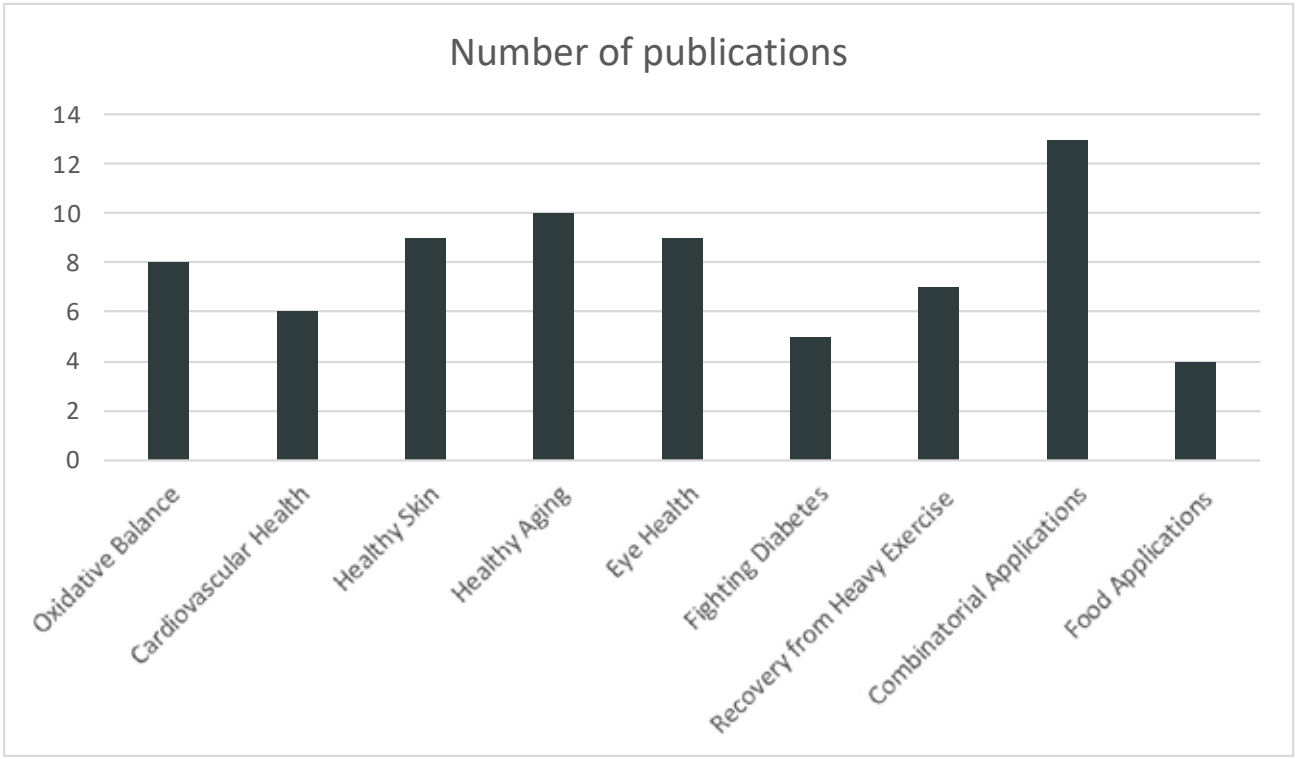
Haematococcus pluvialis extract characterized by component astaxanthin esters has been awarded a GRAS (Generally Regarded As Safe) classification by the United States Food and Drug Administration (FDA). It allows the use of astaxanthin esters from *Haematococcus pluvialis* as a food additive for baked 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.

Astaxanthin is safe to consume and does not elicit side effects.
A significant body of scientific evidence including human and animal studies exists in support safety-in-use for natural astaxanthin.

Factors influencing Astaxanthin bioavailability		Ref.
Consumption	The bioavailability of astaxanthin was 2.4 time higher in the after-meal group compared to 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 from 2 to 4 times.	[16]
Isomers	Astaxanthin exists in optical/configurational and geometric stereo isomer forms. Stereoisomerism exerts a marked influence on the physical properties. Notably, isomeric differences of astaxanthin have been studied mainly in animal models. This is because the natural astaxanthin in human diet comes mainly from microalgae or wild salmonids that feed on algae, and have the same composition of isomers. The distribution of the isomers in natural astaxanthin differs from that of the synthetic product. The optical isomers of astaxanthin accumulate selectively in plasma because they are hydrolyzed depending on the stereochemistry on the 3 and 3'-hydroxygroups. 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 geometric 9Z– and 13Z astaxanthin is lower than for the all-E isomer. Moreover, all-E-isomer accumulate selectively in muscle and plasma, and 13Z-astaxanthin in liver of farmed salmonid fishes.	[15, 17-20]
Esterification	Natural astaxanthin from *Haematococcus pluvialis* is esterified and because of this, it is more stable and easier absorbed into a body.	[21-23]
Other	Tabaco smoke promote astaxanthin degradation leading to reduced bioavailability.	[10]



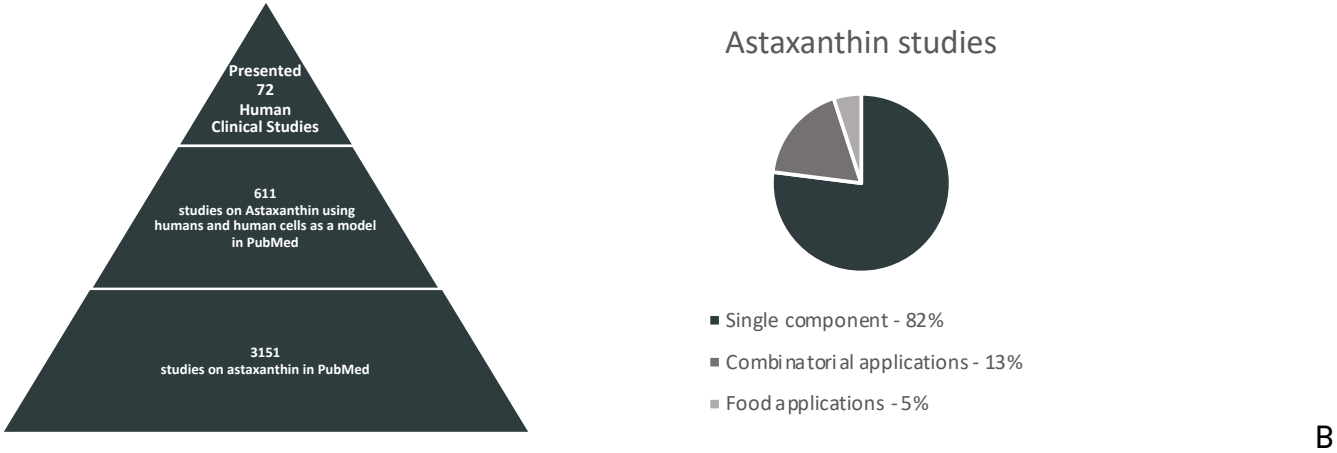


Figure 2.
Overview of research studies on astaxanthin. A. A total number of studies on astaxanthin in PubMed, including studies in vitro and using animal models (search performed in January 2023). B. Clinical studies where astaxanthin has been used as a single component (n=59) or in combination (n=13) with other dietary supplements such as antioxidants and in food applications (n=4).

Overview of Human Clinical Studies using Astaxanthin

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

Astaxanthin has been studied by research groups world-wide 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.

The best source of high-value astaxanthin producers has been found to be microalgae. Algal astaxanthin is widely employed in pharmaceuticals, aquaculture, health foods, cosmetics, and other industries because it has a wide range of bioactivities. Natural astaxanthin remains superior to cheap synthetic astaxanthin for use as food additive for human consumption.

There are over 70 published clinical studies on natural astaxanthin in humans, as well as many in vitro and in vivo studies (Fig. 2A).

In clinical studies, astaxanthin has been mainly used as a single component (82%), although studies with astaxanthin in combination with other nutrients are also available (18%) (Fig.2 B). A thorough examination of astaxanthin sources used in these studies revealed that natural astaxanthin was largely obtained from *Haematococcus pluvialis*. This provides evidence that astaxanthin from algal sources is the best documented when it comes to health benefits.

Health benefits supported by clinical studies natural 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 eye health;**
- **Helps fighting diabetes;**
- **Supports the body in recovery from heavy exercise.**

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.

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

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 Glance	
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 [26].
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. • The expression levels of the specific genes and proteins in the oxidative stress response pathway (Nrf2, HO-1, and NQ-1) • 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 blood.

Substation studies focused on astaxanthin and oxidative balance

Roghaye Gharaei et al. (2022). "Randomized controlled trial of astaxanthin impacts on antioxidant status and assisted reproductive technology outcomes in women with polycystic ovarian syndrome." J Assist Reprod Genet. 2022 Apr;39(4):995-1008. [24]

"Purpose: Polycystic ovary syndrome (PCOS), the most common endocrinopathy in women, is typically accompanied by a defective oxidative defence system. Here, we investigated the effect of astaxanthin (AST) as a powerful antioxidant on the oxidative stress (OS) response and assisted reproductive technology (ART) outcomes in PCOS patients. Methods: In this double-blind, randomized, placebo-controlled trial, PCOS 40 patients were randomly assigned into two groups. The intervention group received 8 mg AST, and the control group received the placebo daily for 40 days. The primary outcomes were the serum and follicular fluid (FF) levels of the OS biomarkers and the expression levels of the specific genes and proteins in the oxidative stress response pathway. The secondary outcomes were considered ART outcomes. Results: According to our findings, a 40-day course of AST supplementation led to significantly higher levels of serum CAT and TAC in the AST group compared to the placebo group. However, there were no significant intergroup differences in the serum MDA and SOD levels, as well as the FF levels of OS markers. The expression of Nrf2, HO-1, and NQ-1 was significantly increased in the granulosa cells (GCs) of the AST group. Moreover, the MII oocyte and high-quality embryo rate were significantly increased in the AST group compared to the placebo group. We found no significant intergroup difference in the chemical and clinical pregnancy rates. Conclusion: AST treatment has been shown to increase both serum TAC levels and activation of the Nrf2 axis in PCOS patients' GCs".

Mami Kaneko et al.(2017). "Protective Effect of Astaxanthin on Vocal Fold Injury and Inflammation Due to Vocal Loading: A Clinical Trial." J Voice. 2017 May;31(3):352-358. [25]

"Objectives: Professional voice users, such as singers and teachers, are at greater risk of developing vocal fold injury from excessive use of voice; thus, protection of the vocal fold is essential. One of the most important factors that aggravates injury is the production of reactive oxygen species at the wound site. The purpose of the current study was to assess the effect of astaxanthin, a strong antioxidant, on the protection of the vocal fold from injury and inflammation due to vocal loading. Study design: This study is an institutional review board-approved human clinical trial. Methods: Ten male subjects underwent a 60-minute vocal loading session and received vocal assessments prior to, immediately after, and 30 minutes postvocal loading (AST(-) status). All subjects were then prescribed 24 mg/day of astaxanthin for 28 days, after which they received the same vocal task and assessments (AST(+) status). Phonatory parameters were compared between both groups. Results: Aerodynamic assessment, acoustic analysis, and GRBAS scale (grade,

roughness, breathiness, asthenia, and strain) were significantly worse in the AST(-) status immediately after vocal loading, but improved by 30 minutes after loading. In contrast, none of the phonatory parameters in the AST(+) status were statistically worse, even when measured immediately after vocal loading. No allergic responses or adverse effects were observed after administration of astaxanthin. Conclusions: The current results suggest that astaxanthin can protect the vocal fold from injury and inflammation caused by vocal loading possibly through the regulation of oxidative stress".

Kim et al. (2011). "Protective effects of Haematococcus astaxanthin on oxidative stress in healthy smokers." J Med Food 14(11): 1469-1475. [26]

"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. [27]

"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. [28]

"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."

Leif Percival Andersen et al. (2007). "Gastric inflammatory markers and interleukins in patients with functional dyspepsia treated with astaxanthin." FEMS Immunol Med Microbiol. 2007 Jul;50(2):244-8. [29]

"The chronic active inflammation caused by Helicobacter pylori is dominated by neutrophils, macrophages, lymphocytes and plasma cells. Several interleukins are involved in the inflammatory process. The aim of this study was to investigate the effect of astaxanthin on gastric inflammation in patients with functional dyspepsia. Forty-four consecutive patients were included, and biopsies were examined for IL-4, IL-6, IL-8, IL-10, interferon-gamma, CD4, CD8, CD14, CD19, CD25 and CD30. Patients were randomized: 21 patients were treated with 40 mg of astaxanthin daily, and 23 patients were treated with a placebo. There was a significant decrease in gastric inflammation in H. pylori-positive patients from both groups. There were no significant changes in the density of H. pylori or in any of the interleukins during or after treatment. There was a significant up-regulation of CD4 and down-regulation of CD8 in patients with H. pylori treated with astaxanthin."

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. [30]

The study focused on oxidative stress in athletes. Abstract is given under Sport Benefit.

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. [31]

The study focused on lipid profiles in blood and oxidative stress. 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. [32]

The study focused on age-related vision degeneration and oxidative stress in the aqueous humor. 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. [33]

The study was 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. [34]

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

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 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 Glance	
Dietary supplementation	• Reduces oxidative stress; • Improves lipid profiles, decreased triglyceride-rich lipoproteins (biomarker of coronary heart disease); • Promotes better blood flow in capillaries.
Dose	6, 8, 12 or 18 mg /day
Time-to-effect	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 paraoxinase. • Inflammation markers, such as interleukin 6 and interleukin 2 receptors and plasma protein C.

Substation 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. [35]

"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. [36]

"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."

Ayoub Saeidi et al. (2023). "Astaxanthin Supplemented with High-Intensity Functional Training Decreases Adipokines Levels and Cardiovascular Risk Factors in Men with Obesity" Nutrients. 2023 Jan 6;15(2):286. [37]

"The aim of this study was to investigate the effects of 12 weeks of high-intensity training with astaxanthin supplementation on adipokine levels, insulin resistance and lipid profiles in males with obesity. Sixty-eight males with obesity were randomly stratified into four groups of seventeen subjects each: control group (CG), supplement group (SG), training group (TG), and training plus supplement group (TSG). Participants underwent 12 weeks of treatment with astaxanthin or placebo (20 mg/d capsule daily). The training protocol consisted of 36 sessions of high-intensity functional training (HIFT), 60 min/sessions, and three sessions/week. Metabolic profiles, body composition, anthropometrical measurements, cardio-respiratory indices and adipokine [Cq1/TNF-related protein 9 and 2 (CTRP9 and CTRP2) levels, and growth differentiation factors 8 and 15 (GDF8 and GDF15)] were measured. There were significant differences for all indicators between the groups ($p < 0.05$). Post-hoc analysis indicated that the levels of CTRP9, CTRP2, and GDF8 were different from CG ($p < 0.05$), although levels of GDF15 were similar to CG ($p > 0.05$). Levels of GDF8 were similar in the SG and TG groups ($p > 0.05$), with reductions of GDF15 levels in both training groups ($p<0.05$). A total of 12 weeks of astaxanthin supplementation and exercise training decreased adipokines levels, body composition (weight, %fat), anthropometrical factors (BMI), and improved lipid and metabolic profiles. These benefits were greater for men with obesity in the TSG group."

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. [31]

"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. [38]

"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."

Supporting studies on astaxanthin and cardiovascular health

Takao Kato et al. (2020). "Effects of 3-Month Astaxanthin Supplementation on Cardiac Function in Heart Failure Patients with Left Ventricular Systolic Dysfunction-A Pilot Study." Nutrients. 2020 Jun; 12(6): 1896. [39]

Correlation between suppression of oxidative stress and improvement of cardiac contractility suggests that suppression of oxidative stress by astaxanthin supplementation had therapeutic potential to improve cardiac functioning.

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. [33]

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

Ines Villano et al. (2022). The Role of Nutraceutical Supplements, Monacolin K and Astaxanthin, and Diet in Blood Cholesterol Homeostasis in Patients with Myopathy. Biomolecules. 2022 Aug 14;12(8):1118. [40]

Study found a significant improvement in total cholesterol, HDL, LDL, PCR and CPK parameters in experimentsl group compared with control group. Our results highlight the efficacy and safety of combined use of monacolin k (5 mg) and astaxanthin (0.1 mg) in combination with a low-energy/fat diet in the treatment of dyslipidemia.

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

The study focused on age-related blood lipid peroxidation and antioxidant status in postmenopausal women. 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. [42]

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

Supports Healthy Skin

The skin is continually exposed to various environmental factors such as air, solar radiation, and pollutants, which can lead to the formation of free radicals. As the skin serves as a protective barrier, it experiences a greater burden of free radicals compared to other organs. Aging further thins the skin layers, increasing its susceptibility to UV radiation and contributing to the formation of free radicals. Exposure to high levels of UV radiation can cause premature aging by reducing skin elasticity and increasing pigmentation. Additionally, free radicals can be generated in the skin due to normal metabolism and inflammation.

Research has investigated the potential benefits of astaxanthin on skin health through dietary supplementation and topical application. Clinical studies have shown that astaxanthin supplementation and the application of creams containing astaxanthin can improve skin appearance, including skin tone, sallowness, and fine lines. The greatest improvements were observed in subjects who used both the supplement and the topical products.

Clinical studies demonstrated that astaxanthin supplementation and/or applying a cream with astaxanthin improved skin appearance including skin tone, fine lines and sallowness.

Astaxanthin Benefits for Skin Health at Glance	
Dietary supplementation and topical applications	• Reduces hyper-pigmentation, 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	8 to12 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 and subjective skin conditions; • Minimal erythema dose (MED); • UV-induced changes of moisture and transepidermal water loss (TEWL);

Substation studies focused on astaxanthin benefits for healthy skin

Naoki Ito et al. (2018.) "The Protective Role of Astaxanthin for UV-Induced Skin Deterioration in Healthy People-A Randomized, Double-Blind, Placebo-Controlled Trial." Nutrients. 2018 Jun 25;10(7):817. [43]

"Skin is a major safeguard tissue in humans. Because biological barrier function is deteriorated by several kinds of stresses including exposure to ultra-violet (UV) rays, the protection and treatment of skin conditions by dietary supplements are important. We therefore evaluated the effects of dietary supplementation with an algal food-derived antioxidant, astaxanthin, on UV-induced skin deterioration. Twenty-three healthy Japanese participants were recruited to a 10-week double-blind placebo-controlled study. They were assigned to the astaxanthin group supplemented with a capsule containing 4 mg of astaxanthin or the placebo group. To assess the protective role of astaxanthin for UV-induced skin deterioration, we determined the minimal erythema dose (MED) and analyzed UV-induced changes of moisture and transepidermal water loss (TEWL) at baseline and after 9 weeks of supplementation. Subjective skin conditions were assessed by the visual analog scale. The astaxanthin group showed increased MED compared with placebo. In addition, the astaxanthin group had a reduced loss of skin moisture in the irradiated area compared with placebo. Subjective skin conditions for “improvement of rough skin” and “texture” in non-irradiated areas were significantly improved by astaxanthin. Astaxanthin seems protective against UV-induced skin deterioration and helps maintain healthy skin in healthy people".

Tominaga et al. (2012). "Cosmetic benefits of astaxanthin on human subjects." Acta Biochim Pol 59(1): 43-47. [44]

"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."

Tominaga, Kumi et al. (2017). "Protective effect of astaxanthin on skin deterioration Journal of Clinical Biochemistry and Nutrition." Open AccessVolume 61, Issue 1, Pages 33 – 39 July 2017. [45]

"Astaxanthin is a carotenoid with potent antioxidant and anti-inflammatory activity. To evaluate the anti-inflammatory effect of astaxanthin on skin deterioration, we confirmed its role in epidermal-dermal interactions in vitro. Astaxanthin treatment suppressed ultraviolet B (UVB)-induced inflammatory cytokine secretion in keratinocytes, and matrix metalloproteinase-1 secretion by fibroblasts cultured in UVB-irradiated keratinocyte medium. To verify these findings, we conducted a 16-week clinical study with 65 healthy female participants. Participants were orally administered either a 6 mg or 12 mg dose of astaxanthin or a placebo. Wrinkle parameters and skin moisture content significantly worsened in the placebo group after 16 weeks. However, significant changes did not occur in the astaxanthin groups. Interleukin-1a levels in the stratum corneum significantly increased in the placebo and low-dose groups but not in the high-dose group between weeks 0 and 16. This study was performed in Japan from August to December, when changing environmental factors, such as UV and dryness, exacerbate skin deterioration. In conclusion, our study suggests that long-term prophylactic astaxanthin supplementation may inhibit age-related skin deterioration and maintain skin conditions associated with environmentally induced damage via its anti-inflammatory effect. (UMIN Clinical Trials Registry ID: UMIN000018550)."

Seiki et al. (2001). "Effects of astaxanthin from *Haematococcus pluvialis* on human skin." Fragrance Journal 2001(12): 98-103. [46]

"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."

Roghaye Gharaei et al. (2022). "Randomized controlled trial of astaxanthin impacts on antioxidant status and assisted reproductive technology outcomes in women with polycystic ovarian syndrome." J Assist Reprod Genet. 2022 Apr;39(4):995-1008. [24]

"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."

Chalyk et al. (2017). "Continuous astaxanthin intake reduces oxidative stress and reverses age-related morphological changes of residual skin surface components in middle-aged volunteers." Nutrition Research Volume 48, December 2017, Pages 40-48. [48]

"Oxidative stress accelerates skin aging, and dietary supplementation with antioxidants may alleviate it. Morphological analysis of the residual skin surface components (RSSCs) allows detecting age-related changes in corneocyte desquamation, microbial presence, and lipid droplet size. We hypothesized that continuous ingestion of carotenoid antioxidant astaxanthin (4 mg/d) for 4 weeks could influence RSCC morphology and evaluated RSSC samples taken from middle-aged subjects before and after this dietary intervention. The study included 31 volunteers (17 men and 14 women) over the age of 40. RSSC samples were collected from the surface of the facial skin at the beginning (day 0) and end (day 29) of the study. In addition, blood samples were taken on days 0, 15, and 29 for measuring plasma levels of malondialdehyde that allowed assessing systemic oxidative stress. The results demonstrated that plasma malondialdehyde consistently decreased during astaxanthin consumption (by 11.2% on day 15 and by 21.7% on day 29). The analysis of RSSC samples has revealed significantly decreased levels of corneocyte desquamation ($P = .0075$) and microbial presence ($P = .0367$) at the end of the study. These phenomena as well as a significant ($P = .0214$) increase in lipid droplet size were more strongly manifested among obese (body mass index >30 kg/m2) subjects. All described RSSC changes correspond to a shift toward characteristics of skin associated with a younger age. The results confirm our hypothesis by demonstrating that continuous astaxanthin consumption produces a strong antioxidant effect resulting in facial skin rejuvenation which is especially pronounced in obese subjects."

Supporting studies on astaxanthin and skin health

Suphattra Trakanwittayarak et al. 4 (2019). "The effect of astaxanthin on allergic contact dermatitis in response to hair dye containing p-phenylenediamine." Eur J Dermatol. 2019 Dec 1;29(6):647-648. [49]

Application of astaxanthin emulsion pre-treatment reduced the allergenic response to p-phenylenediamine-containing hair dye. This study could be beneficial regarding attempts to reduce the burden of allergic contact dermatitis caused by hair dye cosmetics in sensitized subjects.

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. [33]

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 4 and 8 weeks respectively as measured by Anti-Aging QOL Common Questionnaire.

Qin Xiang Ng et al. (2021)."Effects of Astaxanthin Supplementation on Skin Health: A Systematic Review of Clinical Studies" J Diet Suppl. 2021;18(2):169-182. [50]

There is a substantial body of clinical studies examining the effects of AST supplementation on skin health. In many of the randomized, controlled trials reviewed, AST supplementation improved skin texture, appearance (wrinkles), and moisture content at the end of the study period (ranging from 2 to 16 weeks). Further randomized, controlled trials with larger sample sizes and objective dermatological assessments are warranted.

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. [51]

This study evaluated the effects of a rose hip powder made from seeds and shells on 34 healthy subjects, aged 35-65 years. Astaxanthin (dietary supplementation, 4 mg) has been used as a positive control. Both treatments improved aging-induced skin conditions. Astaxanthin had better effect on skin moisture.

Supports Healthy Aging

Natural astaxanthin may slow down or delay aging through reduced oxidative damage.

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, as well as active protein degradation machineries. Aging, on the other hand, is accompanied by mitochondrial dysfunction leading to increased free radical production, which in turn leads to overloading the defence systems and to oxidative damage of cellular components [52]. That is why our body accumulates oxidative damage as we age, and we become more susceptible to several disorders. 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;
- Skin damage;
- Age-related exercise intolerance and reduced quality of life.

Natural astaxanthin may slow down or delay aging through reduced oxidative damage.

Astaxanthin Benefits for Healthy Aging at Glance	
Dietary supplementation	• Delays aging through reduced oxidative damage of blood lipids; • Delays aging through reduced oxidative damage of skin; • Improves cognitive function;
Dose	2, 4, 6, 8 or 12 mg /day
Time-to-effect	4 to 48 weeks
Gender	Females, males
Age	45-82
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, blood diacron-reactive oxygen metabolites (d-ROMs)3 and urinary 8-hydroxy-20 -deoxyguanosine (8-OHdG); • Bi-product of lipid peroxidation, such as phospholipid hydroperoxides and thiobarbituric acid reactive substances; • Superoxide scavenging activity, levels of hydrogen peroxide, and total hydroperoxides; • Cognitive tests; • Exercise tolerance.

Substation studies focused on astaxanthin benefits on antiaging

Sophia Z Liu et al. (2021). "Astaxanthin supplementation enhances metabolic adaptation with aerobic training in the elderly." Physiol Rep. 2021 Jun;9(11):e14887. [53]

"Older adults between the ages of 65 and 82 were recruited through public lectures, mailers, posted advertisements, and referrals from prior studies. Participants attended up to three visits to the laboratory. At baseline (V1) participants performed a graded exercise test (GXT), tibialis anterior (TA) muscle endurance test, and had blood drawn for blood metabolic panel and AX level measurements, before being blindly randomized to the AX or PL group. After one month of supplementation alone, participants returned to the lab (V2) for a blood test and to begin endurance training (ET). Following 12 weeks of ET with continued supplementation of AX or Placebo, participants returned for a final visit (V3) for GXT, blood tests, and TA muscle endurance test. Out of the 58 enrolled participants, 42 completed the TA muscle performance testing (see previous publication for details)(Liu et al., 2018), and 40 completed the graded exercise test (GXT), specifically 17 males and 23 females (one of the female had a high aerobic capacity >2SD higher than the mean and was excluded from analysis). Study demonstrated that combining AX and exercise training leads to improved fat oxidation, CHO sparing, and increased exercise efficiency in aged healthy subjects, especially in males. These metabolic improvements combined with the benefits of the combined intervention on improvements in muscle strength, size, and specific force indicate that incorporation of AX into an exercise training program in the elderly could enhance exercise tolerance and quality of life."

Sophia Z Liu et al. (2017). "Building strength, endurance, and mobility using an astaxanthin formulation with functional training in elderly." J Cachexia Sarcopenia Muscle. 2018 Oct;9(5):826-833. [54]

"Building both strength and endurance has been a challenge in exercise training in the elderly, but dietary supplements hold promise as agents for improving muscle adaptation. Here, we test a formulation of natural products (AX: astaxanthin, 12 mg and tocotrienol, 10 mg and zinc, 6 mg) with both anti-inflammatory and antioxidant properties in combination with exercise. We conducted a randomized, double-blind, placebo-controlled study of elderly subjects (65-82 years) on a daily oral dose with interval walking exercise on an incline treadmill. Methods: Forty-two subjects were fed AX or placebo for 4 months and trained 3 months (3×/week for 40-60 min) with increasing intervals of incline walking. Strength was measured as maximal voluntary force (MVC) in ankle dorsiflexion exercise, and tibialis anterior muscle size (cross-sectional area, CSA) was determined from magnetic resonance imaging. Results: Greater endurance (exercise time in incline walking, >50%) and distance in 6 min walk (>8%) accompanied training in both treatments. Increases in MVC by 14.4% (±6.2%, mean ± SEM, $P < 0.02$, paired t-test), CSA by 2.7% (±1.0%, $P < 0.01$), and specific force by 11.6% (MVC/CSA, ±6.0%, $P = 0.05$) were found with AX treatment, but no change was

evident in these properties with placebo treatment (MVC, 2.9% ± 5.6%; CSA, 0.6% ± 1.2%; MVC/CSA, 2.4 ± 5.7%; P > 0.6 for all). Conclusions: The AX formulation improved muscle strength and CSA in healthy elderly in addition to the elevation in endurance and walking distance found with exercise training alone. Thus, the AX formulation in combination with a functional training programme uniquely improved muscle strength, endurance, and mobility in the elderly."

Jui-Tung Chen et al. (2017). "Effects of Astaxanthin on Liver and Leukocyte Parameters in Healthy Climacteric Women: Preliminary Data." J Med Food. 2017 Jul;20(7):724-725. [55]

"Astaxanthin, a xanthophyll carotenoid and a cellprotective micronutrient (i.e., with antioxidative action), is often used as a dietary supplement among health conscious people. Although astaxanthin is well known to have an antioxidative function, there are also other health benefits (i.e., anti-inflammation, immunomodulation) that are well documented. Thus, the effects of astaxanthin supplementation on health should be further examined; however, there is currently a paucity of data obtained from clinical studies in an evidence-based manner among relatively healthy people. This study aimed to observe the changes in laboratory measures following astaxanthin supplementation among healthy climacteric women (this population generally uses supplementations including astaxanthin). The study was a double-blinded randomized controlled clinical trial (approved by the institute Ethical Committee, UMIN trial No. 000011834) on astaxanthin supplementation for healthy women. Informed consent was obtained from the participants. Inclusion criteria were subjectively healthy women in a climacteric phase. Histories of hormone replacement therapy, current smoking habits, cardiometabolic diseases, and the use of antioxidant supplements comprised the exclusion criteria. Finally, 14 women were administered 12 mg/day astaxanthin, while 15 women received a placebo over a period of 3 months. Their respective laboratory measures were determined during a fast before and after treatment. The examinations of blood samples were conducted in a single center of a nationally certified laboratory (LSI Co. Ltd., Tokyo, Japan). As oxidative stress markers, the levels of blood diacron-reactive oxygen metabolites (d-ROMs)3 and urinary 8-hydroxy-20 -deoxyguanosine (8-OHdG) were determined, while as an antioxidative marker, the levels of biological antioxidant potential (BAP) were determined. In summary, astaxanthin supplementation can be considered to have a protective effect on the liver even in subjectively healthy climacteric women."

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

"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

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. [42]

"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."

Limas Kupcinskas et al. (2008). "Efficacy of the natural antioxidant astaxanthin in the treatment of functional dyspepsia in patients with or without Helicobacter pylori infection: A prospective, randomized, double blind, and placebo-controlled study." Phytomedicine. 2008 Jun;15(6-7):391-9. [56]

The aim of this study was to evaluate the efficacy of the natural antioxidant astaxanthin in functional dyspepsia in different doses and compared with placebo. Study was a controlled, prospective, randomized, and double blind trial. Patients: Patients with functional dyspepsia, divided into three groups with 44 individuals in each group (placebo, 16 mg, or 40 mg astaxanthin, respectively). Interventions: Participants were asked to accept gastroscopy before treatment, together with questionnaires: GSRS and SF-36. Urea breath test (UBT) was done before the treatment. Main outcome: The primary objective was to test the hypothesis that the antioxidant astaxanthin at two doses regimens compared to placebo should ameliorate gastrointestinal discomfort measured as GSRS in patients with functional dyspepsia, who were either positive or negative for Helicobacter pylori, after 4 weeks of treatment. Results: At the end of therapy (week 4) no difference between the three treatment groups was observed regarding mean Gastrointestinal Symptom Rating Scale (GSRS) scores of abdominal pain, indigestion and reflux syndromes. The same results were observed at the end of follow-up. However reduction of reflux syndrome before treatment to week 4 was significantly pronounced in the higher (40 mg) dose compared to the other treatment groups (16 mg and placebo, p=0.04). Conclusion: In general, no curative effect of astaxanthin was found in

functional dyspepsia patients. Significantly greater reduction of reflux symptoms were detected in patients treated with the highest dose of the natural antioxidant astaxanthin. The response was more pronounced in H. pylori-infected patients.

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. [57]

"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."

N. Hongo, et al. (2017). "Daily fatigue-reducing effect of astaxanthin—a randomized, placebo-controlled, double-blind, parallel-group study." Jpn. Pharmacol. Ther., 45 (2017), pp. 67-72. [58]

"To evaluate the effects of astaxanthin on the sense of fatigue occurring in daily life and to investigate the relationship of the fatigue-reducing effect with the antioxidative potential. Method: A 12-week, randomized, placebo-controlled, parallel-group study was conducted. After screening for eligibility, 39 subjects with fatigue were assigned to 2 groups. The astaxanthin group received 12 mg of astaxanthin and 20 mg of tocotrienol, while the control group received 20 mg of tocotrienol alone. All subjects took Uchida-Kraepelin performance tests as mental loading and cycled using a bicycle ergometer as physical loading in Weeks 0, 4 and 8. A visual analog scale (VAS) of perceived fatigue was performed before and after loading. In Weeks 0 and 8, a Profile of Mood States (POMS) questionnaire was performed. The biological antioxidant potential (BAP) was measured with blood samples taken at the screening and in Week 12. Results: Thirty-eight subjects completed the study. Intent-to-treat (ITT) analysis revealed that the sense of fatigue after both physical and mental loading was significantly lower in the astaxanthin group than in the control group in Week 8. The change in Friendliness in POMS was significantly higher in the astaxanthin group than in the control group in Week 8. No significant differences were observed in the change rate in the BAP value in Week 12 between the astaxanthin group and control group. Conclusion: Astaxanthin reduced the daily sense of fatigue caused by both mental and physical loads. No increase in BAP was, however, observed in subjects receiving astaxanthin."

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. [47]

The study focused on astaxanthin and collagen effects on the aging skin. 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. [59]

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. [60]

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

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). [61]

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

Supports Eye Health

Numerous illnesses, including brain and heart ischemia, reperfusion injury following such ischemic events, and tumor growth, involve oxidation processes [62, 63]. As a result, cutting-edge research on antioxidant compounds has intensified. In the realm of ophthalmology, antioxidant therapies have been studied since oxidation has been linked to diseases such age-related macular degeneration (AMD), diabetic retinopathy, uveitis, and cataracts [64, 69].

Visual display terminals (VDTs), like PCs, smartphones, pads and TVs are widely used and essential in modern life. However, it is known that VDT use results in a reduction in blink frequency, dryness of the eye from insufficient blinks, impaired accommodative function, headache, and tense shoulders [66]. In addition, the proportion of people who have subjective physical symptoms such stiff shoulders and eye tiredness rises as the duration of VDT operation does. Light emitting diodes (LEDs) make up the majority of VDT light sources, and exposure to their blue light is thought to cause dry eyes and eye discomfort by producing reactive oxygen species (ROS) in photoreceptor cells over time [73].

As a result, astaxanthin is anticipated to restore ciliary body function by enhancing blood circulation also reduce free radicals which will enhance accommodative function, improve acuity and contrast sensitivity, lessen eye fatigue.

Astaxanthin is anticipated to improve vision by enhancing blood circulation in the eye also reducing free radicals.

Astaxanthin Benefits for Eye Health at Glance	
Dietary supplementation	• Improves vision for display workers; • Improves eye health by increasing capillary blood flow; • Improved accommodation and visual acuity; • Delays age-related vision degeneration by reducing free radicals in the aqueous humor and improving blood flow in capillaries in eye.
Dose	5, 6, 9 or 12 mg /day
Time-to-effect	2 to 4 weeks
Gender	Females, males
Age	38-70
Markers of the effectiveness	• Improved accommodation amplitude; • Increased retinal capillary blood flow; • Alleviated symptoms associated with accommodation ability and subjective asthenopia; • Elevated choroidal blood flow velocity; • Vascular endothelial growth factor levels; • Superoxide scavenging activity, levels of hydrogen peroxide and total hydroperoxides.

Substation studies focused on astaxanthin benefits on eye health

Yasunori Nagaki et al. (2002). "Effects of astaxanthin on accommodation, critical flicker fusion, and pattern visual evoked potential in visual display terminal workers." J.Trad.Med.19, 170-173, 2002. [65]

"We evaluated the effects of astaxanthin, a red carotenoid, on accommodation, critical flicker fusion (CFF), and pattern visual evoked potential (PVEP) in visual display terminal (VDT) workers. As controls, 13 non-VDT workers received no supplementation (Group A). Twenty-six VDT workers were randomized into 2 groups: Group B consisted of 13 subjects who received oral astaxanthin, 5 mg/day, for 4 weeks, and Group C consisted of 13 subjects who received an oral placebo, 5 mg/day, for 4 weeks. No significant difference in age was noted among the 3 groups. A double-masked study was designed in Groups B and C. Accommodation aqilitude in Group A was 3.72±1.5 diopters. Accommodation amplitudes (2.3±1.4 and 2.2±1.0 diopters) in Groups B and C before supplementation were significantiy ($p<0.05$) lower than in Group A. Accommodation amplitude (2.82±1.6 diopters) in Group B after astaxanthin treatment was significantly ($p<0.01$) larger than before supplementation, while accommodation amplitude (2.32±1.1 diopters) in Group C after placebo supplementation was unchanged. The CFFs and amplitude and latency of P100 in PVEP in Group A were 45.0±4.2 Hz, 6.54±1.8 μV, and 101.3±6.5 msec, respectively. The CFFs in Groups B and C before supplementation were significantly ($p<0.05$) lower than in Group A. The CCFs in Groups B and C did not change after supplementation. Amplitudes and latencies of P100 in PVEP in Groups B and C before supplementation were similar to those in Group A and did not change after supplementation. Findings of the present study indicated that accommodation amplitude improved after astaxanthin supplementation in VDT workers."

YASUNORI Nagaki et al. (2005). "The effect of astaxanthin on retinal capillary blood flow in normal volunteers." Transl. J. Clin. Ther. Med., Vol. 21 (Issue 5) (2005). [66]

"We evaluated the effect of astaxanthin on retinal circulation in healthy volunteers. Design: A double blind randomized placebo controlled study. Methods : Thirty-six volunteers were randomized into two groups: An astaxanthin group that consisted of 18 subjects who received oral astaxanthin, 6mg/day, for 4 weeks and a placebo group that consisted of 18 subjects who received an identical looking oral placebo for 4 weeks. Retinal capillary blood flow was measured using a Heidelberg Retina Flowmeter. Changes in blood pressure, blood cell counts, fasting plasma glucose level, fasting plasma astaxanthin level, retinal capillary blood flow and intraocular pressure were examined and a survey about eye strain taken before and after supplementation in both groups. Results : The fasting plasma astaxanthin level in the astaxanthin group was significantly ($p<0.001$) higher than before supplementation. The fasting plasma astaxanthin level in the placebo group after placebo treatment remained unchanged. After 4 weeks supplementation, retinal capillary blood flow in the astaxanthin group was significantly ($p<0.01$) higher than before supplementation in both eyes, while retinal capillary blood flow in the placebo group after

placebo treatment was unchanged. Intraocular pressures in both groups remained unchanged during the supplementation period. Conclusion: Our results suggest that astaxanthin supplementation may increase retinal capillary blood flow."

Y. Nagaki et al. (2006). "Effect of Astaxanthin on Accommodation and Asthenopia." J. Clin. Ther. Med., 22 (1) (2006), pp. 41-54. [67]

"To investigate the effects of astaxanthin (AX) on accommodation and subjective asthenopia. Subjects and Methods: The subjects were patients who had been occupationally engaged in work requiring the use of a visual display terminal (VDT) for 6 h or more per day for more than 1 year and who frequently experienced asthenopia. They were recruited and provided informed consent. For objective assessment of the clinical trials, we employed a double-blind placebo controlled design where the results of the dietary supplements (AX) group were compared with those of the control (placebo) group. After consumption of AX for 4 weeks, an evaluation was made on the pre-and post-treatment accommodation ability, and the patients were asked to complete a questionnaire to report their subjective asthenopia. In parallel, the safety of astaxanthin was assessed through a clinical examination and a doctor's questionnaire Results: (1) The post-treatment accommodation ability of the AX group with respect to value and rate of change was significantly higher than that of the control group. (2) The distribution of rate of change also showed significant improvement in post-treatment accommodation ability of the AX group when compared to control group. (3) Subjective questionnaire regarding 4 conditions ("eyestrain", "hazy vision", "flickering images", "my shoulders/back feel stiff"), showed that AX group significantly improved to those of control group. (4) Clinical examinations revealed no clinically relevant abnormal changes resulting from AX consumption. Furthermore, there were no reports of adverse events associated with AX consumption. Conclusion: Here we demonstrated that AX consumption (9 mg per day) for 4 weeks substantially alleviated symptoms associated with accommodation ability and subjective asthenopia. Moreover, no safety problems associated with AX consumption were found."

Saito et al. (2012). "Astaxanthin increases choroidal blood flow velocity." Graefes Arch Clin Exp Ophthalmol 250(2): 239-245. [68]

"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."

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. [69]

"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. [32]

"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."

Supporting studies on astaxanthin and eye health

Nakamura A. et al. (2004). "Changes in visual function following peroral astaxanthin." Japanese Journal of Clinical Ophthalmology, 2004. 58(6): p. 1051-1054. [70]

After ingestion of astaxanthin for consecutive 28 days, the uncorrected far visual acuity significantly improved in groups receiving 4 mg or 12 mg. The accommodation time significantly shortened in groups receiving 4 mg or 12 mg. There was no change in refraction, flicker fusion frequency, or pupillary reflex. Study mentioned in "Additional studies" section.

Iwasaki, T. et al. (2006). "Effects of Astaxanthin on Eyestrain Induced by Accommodative Dysfunction." Journal of the Eye, 2006. 23(6): p. 826-834. Cyanotech corporation. [71]

The symptoms eye fatigue, eye heaviness, blurred vision and eye dryness in P group were increased, but Ax group showed increased in eye fatigue and eye heaviness. On the basis of these results, we concluded that astaxanthin has the effects of reducing and preventing eyestrain induced by accommodative dysfunction. Study mentioned in "Additional studies" section.

Takahashi Nanako et al. (2005). "Effects of Astaxanthin on Accommodative Recovery" Journal of Clinical Therapeutics & Medicines), Vol.21, Issue 4, 431-436. Cyanotech corporation. [72]

We have examined the effects of AX on accommodative recovery from rest after operation. Ten healthy volunteers participated in the study. One subject was removed from the study as that person developed allergic conjunctivitis during the study. Therefore, only nine volunteers were evaluated (9 dominant eyes) based the objective diopter value, the HFC value, and the accommodative reaction value. The result showed the HFC value after operation decreased significantly after AX intake compared to that of before uptake. This study suggested that AX had effect on accommodation and worked on accommodative fatigue during the recovery process, which aided in relieving fatigue rapidly. Study mentioned in "Additional studies" section.

Yuki Kizawa et al. (2021). "Effects of anthocyanin, astaxanthin, and lutein on eye functions: a randomized, double-blind, placebo-controlled study." J Clin Biochem Nutr. 2021 Jul; 69(1): 77–90. [73]

6-weeks consumption of the test food inhibited a decrease in the accommodative function caused by visual display terminal operation (UMIN000036989). Study is presented in "Combinatorial applications of astaxanthin" section.

Jehn-Yu Huang et al. (2016). "A randomized, double-blind, placebo-controlled study of oral antioxidant supplement therapy in patients with dry eye syndrome." Clin Ophthalmol. 2016 May 9;10:813-20. [74]

Oral antioxidant supplementations may increase tear production and improve tear film stability by reducing tear ROS. The vegetable-based antioxidant supplement used in this study is safe and can be utilized as an adjuvant therapy to conventional artificial tear therapy for patients with dry eye syndrome. Study is presented in "Combinatorial applications of astaxanthin" section.

Vincenzo Parisi et al. (2008). "Carotenoids and antioxidants in age-related maculopathy italian study: multifocal electroretinogram modifications after 1 year." Ophthalmology. 2008 Feb;115(2):324-333.e2. [75]

In nonadvanced age-related macular degeneration eyes, a selective dysfunction in the central retina (0 degrees -5 degrees) can be improved by the supplementation with carotenoids and antioxidants. No functional changes are present in the more peripheral (5 degrees -20 degrees) retinal areas. Study is presented in "Combinatorial applications of astaxanthin" section.

Stefano Piermarocchi et al. (2012). "Carotenoids in Age-related Maculopathy Italian Study (CARMIS): two-year results of a randomized study." Eur J Ophthalmol. 2012 Mar-Apr;22(2):216-25. [76]

Patients treated with lutein/zeaxanthin and astaxanthin together with other nutrients were more likely to report clinically meaningful stabilization/improvements in visual acuity, contrast sensitivity, and visual function through 24 months compared with nontreated subjects. Further studies are needed with more patients and for longer periods of time. Study is presented in "Combinatorial applications of astaxanthin" section.

Keiko Kono et al. (2014). "Effect of Multiple Dietary Supplement Containing Lutein, Astaxanthin, Cyanidin-3-Glucoside, and DHA on Accommodative Ability." Curr Med Chem. 2014 Aug; 14(2): 114–125. [77]

This study shows that multiple dietary supplement containing lutein, astaxanthin, cyanidin-3-glucoside, and DHA has effect to improve accommodative ability and subjective symptoms related to eye fatigue. Study is presented in "Combinatorial applications of astaxanthin" section.

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). [61]

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

Helps Fighting Diabetes

Antioxidants such as astaxanthin helps to prevent or ameliorate diabetes and its subsequent complications.

Diabetes mellitus (DM), the most common metabolic disease, has become a major health concern with increasing prevalence worldwide. DM is a chronic disease that is recognized by hyperglycemia (HG) resulting from impaired insulin secretion, inappropriate insulin action, or both. The insulin deficit leads to high levels of blood glucose (HG), which, if not tightly controlled, leads to disabling and life-threatening health complications including cardiovascular diseases, retinopathy, neuropathy, nephropathy, and prolonged/incomplete wound healing [78].

The development of DM and its complications are known to be associated with oxidative stress (OS) and low-grade chronic inflammation. OS, an imbalance between cellular oxidant and antioxidant systems, results from the overproduction of free radicals and associated reactive oxygen species (ROS). HG upregulates the markers of chronic inflammation and contributes to increased ROS generation, which ultimately involves DM complications including vascular dysfunction [79]. Moreover, an increased level of ROS reduces insulin secretion and impairs insulin sensitivity and signalling in insulin-responsive tissues [80]. Proper treatment of HG and inhibition of ROS overproduction is, therefore, crucial for delaying the DM onset and progression as well as for preventing its subsequent complications [81-83].

Recent advances in biological properties of antioxidants such as carotenoids have suggested that these compounds are not only able to prevent but also able to ameliorate diabetes and its subsequent complications [84].

Astaxanthin Helps Fighting Diabetes at Glance	
Dietary supplementation	• Have preventive effects against diabetes and atherosclerosis; • Beneficial for improving circulating MDA and IL-6 and the down-regulation of miR-146a. • Reduced the fructosamine concentration ($p<0.05$) and marginally reduced the plasma glucose concentration. • Improve oxidative stress and certain inflammation biomarkers, particularly in T2DM patients.
Dose	8-12 mg/day
Time-to-effect	8 to 12 weeks
Gender	Females, males
Age	20-70
Markers of the effectiveness	• Reduced levels of HbA1c , apo E and malondialdehyde-modified low-density lipoprotein. • Decresed levels MDA and IL-6 and miR-146a. • Reduced the fructosamine concentration ($p<0.05$) and marginally reduced the plasma glucose.

Substation studies focused on astaxanthin fighting diabetes

Masaharu Urakaze et al. (2021). "The Beneficial Effects of Astaxanthin on Glucose Metabolism and Modified Low-Density Lipoprotein in Healthy Volunteers and Subjects with Prediabetes." Nutrients. 2021 Dec 7;13(12):4381. [85]

"Astaxanthin (ASTX) is an antioxidant agent. Recently, its use has been focused on the prevention of diabetes and atherosclerosis. We examined the effects of astaxanthin supplementation for 12 weeks on glucose metabolism, glycemic control, insulin sensitivity, lipid profiles and anthropometric indices in healthy volunteers including subjects with prediabetes with a randomized, placebo-controlled trial. Methods: We enrolled 53 subjects who met our inclusion criteria and administered them with 12 mg astaxanthin or a placebo once daily for 12 weeks. Subsequently, their HbA1c levels, lipid profiles and biochemical parameters were determined. The participants also underwent a 75 g oral glucose tolerance test (OGTT), vascular endothelial function test and measurement of the visceral fat area. Results: After astaxanthin supplementation for 12 weeks, glucose levels after 120 min in a 75 g OGTT significantly decreased compared to those before supplementation. Furthermore, the levels of HbA1c (5.64 ± 0.33 vs. 5.57 ± 0.39%, $p < 0.05$), apo E (4.43 ± 1.29 vs. 4.13 ± 1.24 mg/dL, $p < 0.05$) and malondialdehyde-modified low-density lipoprotein (87.3 ± 28.6 vs. 76.3 ± 24.6 U/L, $p < 0.05$) were also reduced, whereas total cholesterol (TC), triglyceride (TG) and high-density lipoprotein-C (HDL-C) levels were unaltered. The Matuda index, which is one of the parameters of insulin resistance, was improved in the ASTX group compared to that before supplementation. Conclusions: our results suggest that ASTX may have preventive effects against diabetes and atherosclerosis and may be a novel complementary treatment option for the prevention of diabetes in healthy volunteers, including subjects with prediabetes, without adverse effects."

Nafiseh Shokri-Mashhadi et al. (2021). "The antioxidant and anti-inflammatory effects of astaxanthin supplementation on the expression of miR-146a and miR-126 in patients with type 2 diabetes mellitus: A randomised, double-blind, placebo-controlled clinical trial." Int J Clin Pract. 2021 May;75(5):e14022. [86]

"The pathogenesis of type 2 diabetes mellitus (T2DM) is associated with chronic oxidative stress and inflammation. It is well known that the expression of some miRNAs such as miRNA-146a is upregulated in diabetic and hyperglycaemic patients, whereas circulating miRNA-126 is reduced. Therefore, we aimed to determine the effects of astaxanthin (AST) supplementation on the circulating malondialdehyde (MDA) and interleukin 6 (IL-6) levels, and the expression of miR-146a and miR-126 in patients with T2DM. Methods: This randomised, double-blind, placebo-controlled clinical trial was conducted in 44 patients with T2DM randomly receiving 8 mg/d of oral AST (n = 22) or placebo (n = 22) for 8 weeks. Results: We observed that AST supplementation could decrease plasma levels of MDA and IL-6 ($P < .05$) and decrease the expression

level of miR-146a over time (fold change: -1/388) (P < .05). Conclusion: AST supplementation might be beneficial for improving circulating MDA and IL-6 and the down-regulation of miR-146a. However, future investigations are suggested to confirm these results."

Nafiseh Sokri Mashhadi et al. (2018). "Astaxanthin improves glucose metabolism and reduces blood pressure in patients with type 2 diabetes mellitus." Asia Pac J Clin Nutr. 2018;27(2):341-346. [87]

"This randomized, placebo-controlled trial was performed for 8 weeks to investigate the potential effects of astaxanthin (AST) supplementation on the adiponectin concentration, lipid peroxidation, glycemic control, insulin sensitivity, and anthropometric indices in participants with type 2 diabetes mellitus. Methods and study design: We enrolled 44 participants with type 2 diabetes who met our inclusion criteria. Eight milligrams of AST supplementation or a placebo were randomly administered once daily for 8 weeks to these participants. Results:The 8-week administration of AST supplementation increased the serum adiponectin concentration and reduced visceral body fat mass ($p<0.01$), serum triglyceride and very-low-density lipoprotein cholesterol concentrations, and systolic blood pressure ($p<0.05$). Furthermore, AST significantly reduced the fructosamine concentration ($p<0.05$) and marginally reduced the plasma glucose concentration ($p=0.057$). Conclusions: We demonstrated that because participants with type 2 diabetes often have hypertriglycemia and uncontrolled glucose metabolism; our findings of dual beneficial effects are clinically valuable. Our results may provide a novel complementary treatment with potential impacts on diabetic complications without adverse effects."

Supporting studies on astaxanthin benefits on fighting diabetes

Baolan Ma et al. (2022). "Astaxanthin supplementation mildly reduced oxidative stress and inflammation biomarkers: a systematic review and meta-analysis of randomized controlled trials." Nutr Res. 2022 Mar;99:40-50. [88]

The current work indicated that astaxanthin supplementation may be beneficial for improving oxidative stress and certain inflammation biomarkers, particularly in T2DM patients.

Wei Xia et al. (2020). "The effects of astaxanthin supplementation on obesity, blood pressure, CRP, glycemic biomarkers, and lipid profile: A meta-analysis of randomized controlled trials." Pharmacol Res. 2020 Nov;161:105113. [89]

Systematic review and meta-analysis revealed that astaxanthin consumption was associated with increase in HDL-C ("good cholesterol" – ed.note) and decrease in CRP (blood test that checks for inflammation in the body – ed.note).

Supports the Body in Recovery from Heavy Exercise

Natural astaxanthin improves muscle function by reducing free radical damage and oxidative stress.

Natural astaxanthin has a strong potential in sports nutrition. As an antioxidant, astaxanthin transported throughout the body to all 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 is formed as a bi-product [90]. Free radicals can damage the muscles and reduce their ability to contract [77]. It has been shown that athletes have increased free radical levels in the blood and lower levels of antioxidants [1].

One of the reasons why heavy exercise has negative effects is that free radical formation exceeds the capacity of antioxidant defence 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), a variety of different free radicals compounds are formed [75]. Oxidative stress is implicated in the development of muscle pain, weakness and fatigue.

Natural astaxanthin improves muscle function by reducing free radical damage.

Astaxanthin Benefits for Athletes at Glance	
Dietary supplementation	• Improves muscle endurance and strength; • Prevents muscle fatigue; • Prevents exercise-induced free radical production; • Inhibits the formation of lactic acid.
Dose	4 - 12 mg /day
Time-to-effect	1 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 content of total -SH groups and thiobarbituric acid-reactive substances.

Substation studies focused on astaxanthin benefits the body's in recovery from heavy exercise

Daniel R Brown et al. (2021). "The effect of astaxanthin supplementation on performance and fat oxidation during a 40 km cycling time trial." J Sci Med Sport. 2021 Jan;24(1):92-97. [91]

"This study aimed to investigate whether supplementation with 12 mg·day-1 astaxanthin for 7 days can improve exercise performance and metabolism during a 40 km cycling time trial. Design: A randomised, double-blind, crossover design was employed. Methods: Twelve recreationally trained male cyclists (VO2peak: 56.5 ± 5.5 mL·kg-1·min-1, Wmax: 346.8 ± 38.4 W) were recruited. Prior to each experimental trial, participants were supplemented with either 12 mg·day-1 astaxanthin or an appearance-matched placebo for 7 days (separated by 14 days of washout). On day 7 of supplementation, participants completed a 40 km cycling time trial on a cycle ergometer, with indices of exercise metabolism measured throughout. Results: Time to complete the 40 km cycling time trial was improved by 1.2 ± 1.7% following astaxanthin supplementation, from 70.76 ± 3.93 min in the placebo condition to 69.90 ± 3.78 min in the astaxanthin condition (mean improvement = 51 ± 71 s, p = 0.029, g = 0.21). Whole-body fat oxidation rates were also greater (+0.09 ± 0.13 g·min-1, p = 0.044, g = 0.52), and the respiratory exchange ratio lower (-0.03 ± 0.04, p = 0.024, g = 0.60) between 39-40 km in the astaxanthin condition. Conclusions: Supplementation with 12 mg·day-1 astaxanthin for 7 days provided an ergogenic benefit to 40 km cycling time trial performance in recreationally trained male cyclists and enhanced whole-body fat oxidation rates in the final stages of this endurance-type performance event."

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. [92]

"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. [30]

"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. [93]

"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. [94]

"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 strength endurance - A double blind placebo controlled study on male students. ." Carotenoid Science 13: 20-22. [95]

"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."

Supporting study on astaxanthin and body recovery from heavy exercise

Matthew J McAllister et al. (2022). “Astaxanthin Supplementation Increases Glutathione Concentrations but Does Not Impact Fat Oxidation During Exercise in Active Young Men.” Int J Sport Nutr Exerc Metab . 2022 Jan 1;32(1):8-15. [96]

In this randomized controlled study astaxanthin supplementation of 6 mg/day for 4 weeks increased whole blood levels of the antioxidant glutathione in active young men but did not affect oxidative stress markers or substrate utilization during exercise. Opposite results regarding fat oxidation were obtained by Daniel R Brown (2021) mentioned above when using 12 mg/day, however, in this study astaxanthin appears to be an effective agent to increase endogenous antioxidant status.

Combinatorial Applications of Astaxanthin

Combinatory usage of natural ingredients may provide synergistic/ additive effect for neutralizing free radicals.

Combinatory usage of natural ingredients may provide synergistic/ additive effect for neutralizing free radicals. This could be achieved indirectly by increasing astaxanthin bioavailability combining it with lipophilic ingredients (such as fish oil, Perilla seed oil or sunflower-based phospholipids) and increasing the absorption. The alternative, direct approach would be a combination of ingredients with synergistic actions. This a relatively new and involving research field even the idea of antioxidant network was proposed some years ago [97-98]. 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 if they are water or lipid soluble. For example, water-based vitamin C and glutathione protect cell nucleus. Astaxanthin is lipid soluble, it has a special affinity for cell membranes. However, vitamin C and glutathione turn into weak free radicals after disarming free radicals. Astaxanthin can recycle them back into their active antioxidant form. This rescue-and-revive cycle prolongs the lifespan of these antioxidants and have an additive support for neutralizing free radicals. Notably, astaxanthin never become oxidized by free radicals. Some other nutrients such as polyphenols and minerals may function not solely as antioxidants but may have a supporting role.

Complex dietary supplements containing astaxanthin increased total antioxidant capacity of plasma, reduced lipid peroxidation and improved lipid profiles in large clinical studies [65, 71, 75-76]. High dose of astaxanthin in combination with EPA and vitamin E have been successfully tested as a medical food for the management of elevated triacylglycerol [107].

Roberto Corsi et al. (2018). "A Polyphenol-Based Multicomponent Nutraceutical in Dysmetabolism and Oxidative Stress: Results from a Pilot Study." J Diet Suppl 2018 Jan 2;15(1):34-41. [99]

"To assess short-term efficacy and safety of a multicomponent nutraceutical (MCN) on dysmetabolism and oxidative stress, a pilot prospective observational study was performed on 21 individuals (12 men and 9 women) who took, for 60 days, 2 tablets per day of an MCN based on antioxidants and metabolism regulators: hydroxytyrosol (15 mg), maqui (300 mg), amla (200 mg), monacolin K (10 mg), berberine (245 mg), astaxanthin (0.5 mg), coenzyme Q10 (100 mg), and folic acid (200 mcg). On day 0 (T0) and day 60 (T60), all participants underwent laboratory tests related to lipid profile, carbohydrate metabolism, oxidative stress, and cellular inflammation. Statistical analysis was applied to the resulting data. A significant improvement of most atherogenesis and oxidative stress biomarkers was recorded (mean figure at T0 and T60, p value): total cholesterol 243.50/194.83 mg/dl, p =.0002; low-density lipoproteins 174.50/124.58 mg/dl, p =.0001; glycemia 96.25/88.50 mg/dl, p =.035; total free radicals 306.44/280.93 U.Carr., p =.036; serum antioxidant capacity 2103.00/2246.06 umol/l, p =.0042; oxidized cholesterol 680.33/597.25 uEq/l, p =.0511. Insulinemia, microalbuminuria, high-density lipoproteins, C-reactive protein, and triglycerides had no statistically significant variation. Body weight and systo-diastolic pressure showed no significant change from T0 to T60. No relevant side effects were reported. The investigated MCN (Eonlipid), based on polyphenols, significantly improved the oxidative stress parameters and decreased the majority of atherogenesis parameters at short term. No significant side effects were reported. Further placebo-controlled studies should possibly corroborate the promising results of this pilot study."

Ayano Imai et al. (2018). "Effects of Dietary Supplementation of Astaxanthin and Sesamin on Daily Fatigue: A Randomized, Double-Blind, Placebo-Controlled, Two-Way Crossover Study." Nutrients. 2018 Feb 28;10(3):281. [100]

"Severe fatigue can negatively affect quality of life, and oxidative stress may play a role in its mechanism. The aim of this study was to evaluate the effect of dietary supplementation of astaxanthin and sesamin (AS), strong food-derived antioxidants, on fatigue. Twenty-four healthy volunteers were supplemented with AS and placebo, each for four weeks. After each supplementation period, participants underwent tasks inducing mental and physical fatigue (visual display terminal task and ergometer task, respectively). Subjective fatigue was evaluated using a visual analogue scale during and after the mental and physical tasks, and daily subjective fatigue was evaluated by the Chalder fatigue questionnaire. Secondary outcomes included other subjective feelings, work efficiency, autonomic nerve activity, levels of an oxidative stress marker (plasma phosphatidylcholine hydroperoxide (PCOOH)) and safety. AS supplementation was associated with significantly improved recovery from mental fatigue compared with placebo. Increased PCOOH levels during mental and physical tasks were attenuated by AS supplementation. No differences between AS and placebo were detected in secondary outcomes, and no adverse effects of AS supplementation were observed. In conclusion, AS supplementation may be a candidate to promote recovery from mental fatigue which is experienced by many healthy people."

Yuki Kizawa et al. (2021). "Effects of anthocyanin, astaxanthin, and lutein on eye functions: a randomized, double-blind, placebo-controlled study." J Clin Biochem Nutr. 2021 Jul; 69(1): 77–90. [73]

"We examined the effects of a test food containing anthocyanin, astaxanthin, and lutein on the eye function in healthy Japanese adults with eye fatigue after operating visual display terminals. Forty-four subjects were randomly but equally assigned to the active or placebo group. Two active or placebo capsules were taken once daily for 6 weeks. Accommodative function, tear film break-up time, visual acuity, the value of Schirmer's test, macular pigment optical density level, muscle hardness, and a questionnaire were evaluated before and after a 6-week intervention. Each group included 20 subjects in the efficacy analysis. The active group showed a significant improvement in the percentage of pupillary response of an average of both eyes and dominant eye pre- and post-visual display terminal operation at 6 weeks compared with the placebo group. Moreover, the active group showed a significant improvement in the scores of "A sensation of trouble in focusing the eyes" and "Difficulty in seeing objects in one's hand and nearby, or fine print" compared with the placebo group between before and after ingestion. Therefore, 6-weeks consumption of the test food inhibited a decrease in the accommodative function caused by visual display terminal operation (UMIN000036989)."

Jehn-Yu Huang et al. (2016). "A randomized, double-blind, placebo-controlled study of oral antioxidant supplement therapy in patients with dry eye syndrome." Clin Ophthalmol. 2016 May 9;10:813-20. [74]

"To evaluate the efficacy of oral antioxidant supplementation in the treatment of patients with dry eye syndrome (DES). Methods: A prospective, randomized, double-blinded study compared the effects of an antioxidant supplement (containing anthocyanosides, astaxanthin, vitamins A, C, and E, and several herbal extracts, including Cassiae semen and Ophiopogonis japonicus) with placebo on patients with DES. We assessed dry eye symptoms, visual acuity, Schirmer's test, tear film breakup time, cornea and conjunctiva fluorescein staining, serum anti-SSA/anti-SSB antibodies, and the level of reactive oxygen species (ROS) in tears. The supplementation period was 8 weeks and patients were followed up every 4 weeks for 16 weeks. A linear mixed model was used to compare the groups, while within-group differences were tested by repeated-measures analysis of variance. Results: Forty-three patients, 20 and 23 in treatment and placebo groups, respectively, completed the study. Liver and renal functions were normal. Diastolic blood pressure decreased in the treatment group. There were no significant differences in systolic blood pressure, dry eye symptoms, serum anti-SSA and anti-SSB, visual acuity, intraocular pressure, or fluorescein corneal staining between the groups. Tear film breakup time scores and Schirmer's test without topical anesthesia significantly improved in the treatment group. Tear ROS level differed between the groups and decreased after treatment. Overall subjective impression revealed a significant improvement with treatment compared with placebo. Conclusion: Oral antioxidant supplementations may increase tear production and improve tear film stability by reducing tear ROS. The vegetable-based antioxidant supplement used in this study is safe and can be utilized as an adjuvant therapy to conventional artificial tear therapy for patients with DES."

Vincenzo Parisi et al. (2008). "Carotenoids and antioxidants in age-related maculopathy italian study: multifocal electroretinogram modifications after 1 year." Ophthalmology. 2008 Feb;115(2):324-333.e2. [75]

"To evaluate the influence of short-term carotenoid and antioxidant supplementation on retinal function in nonadvanced age-related macular degeneration (AMD). Design: Randomized controlled trial. Participants: Twenty-seven patients with nonadvanced AMD and visual acuity > or =0.2 logarithm of the minimum angle of resolution were enrolled and randomly divided into 2 age-similar groups: 15 patients had oral supplementation of vitamin C (180 mg), vitamin E (30 mg), zinc (22.5 mg), copper (1 mg), lutein (10 mg), zeaxanthin (1 mg), and astaxanthin (4 mg) (AZYR SIFI, Catania, Italy) daily for 12 months (treated AMD [T-AMD] group; mean age, 69.4+/-4.31 years; 15 eyes); 12 patients had no dietary supplementation during the same period (nontreated AMD [NT-AMD] group; mean age, 69.7+/-6.23 years; 12 eyes). At baseline, they were compared with 15 age-similar healthy controls. Methods: Multifocal electroretinograms in response to 61 M-stimuli presented to the central 20 degrees of the visual field were assessed in pretreatment (baseline) conditions and, in nonadvanced AMD patients, after 6 and 12 months. Main outcome measures: Multifocal electroretinogram response amplitude densities (RAD, nanovolt/deg(2)) of the N1-P1 component of first-order binary kernels measured from 5 retinal eccentricity areas between the fovea and midperiphery: 0 degrees to 2.5 degrees (R1), 2.5 degrees to 5 degrees (R2), 5 degrees to 10 degrees (R3), 10 degrees to 15 degrees (R4), and 15 degrees to 20 degrees (R5). Results: At baseline, we observed highly significant reductions of N1-P1 RADs of R1 and R2 in T-AMD and NT-AMD patients when compared with healthy controls (1-way analysis of variance P<0.01). N1-P1 RADs of R3-R5 observed in T-AMD and NT-AMD were not significantly different (P>0.05) from controls. No significant differences (P>0.05) were observed in N1-P1 RADs of R1-R5 between T-AMD and NT-AMD at baseline. After 6 and 12 months of treatment, T-AMD eyes showed highly significant increases in N1-P1 RADs of R1 and R2 (P<0.01), whereas no significant (P>0.05) change was observed in N1-P1 RADs of R3-R5. No significant (P>0.05) changes were found in N1-P1 RADs of R1-R5 in NT-AMD eyes. Conclusions: In nonadvanced AMD eyes, a selective dysfunction in the central retina (0 degrees -5 degrees) can be improved by the supplementation with carotenoids and antioxidants. No functional changes are present in the more peripheral (5 degrees -20 degrees) retinal areas."

Stefano Piermarocchi et al. (2012). "Carotenoids in Age-related Maculopathy Italian Study (CARMIS): two-year results of a randomized study." Eur J Ophthalmol. 2012 Mar-Apr;22(2):216-25. [76]

"The high concentration of carotenoids in the macula, plus evidence linking oxidative stress to age-related macular degeneration (AMD) and carotenoids to antioxidation, generated the hypothesis that higher antioxidant intakes can prevent AMD. The aim of this study was to determine whether nutritional supplementation with a targeted nutritional supplement improves visual acuity and visual function in AMD. Methods: In this multicenter, prospective open-label randomized study, 145 patients were randomly assigned to 2 different treatment groups. Interventions were lutein (10 mg), zeaxanthin (1 mg), astaxanthin (4 mg; AZYR SIFI, Catania, Italy), and antioxidants/vitamins supplementation formula or no dietary supplementation for 2 years. Primary outcome was mean changes in visual acuity (VA) at 12 and 24

months. Other measures included contrast sensitivity (CS) and National Eye Institute visual function also questionnaire (NEI VFQ-25) scores at 12 and 24 months. Results: Patients in the treated group showed stabilization of VA with significantly (p=0.003) better VA scores (81.4 ± 7.2) compared to the nontreated group (76.8 ± 8.9) at 24-month follow-up. An improvement in CS (p=0.001) and final mean NEI VFQ-25 composite scores at 12 and 24 months higher in treated group compared to nontreated group were also shown (p<0.001). Conclusions: Patients treated with lutein/zeaxanthin and astaxanthin together with other nutrients were more likely to report clinically meaningful stabilization/improvements in VA, CS, and visual function through 24 months compared with nontreated subjects. Further studies are needed with more patients and for longer periods of time."

Naoki Ito at al. (2018). "Effects of Composite Supplement Containing Astaxanthin and Sesamin on Cognitive Functions in People with Mild Cognitive Impairment: A Randomized, Double-Blind, Placebo-Controlled Trial." J Alzheimers Dis. 2018; 62(4): 1767–1775. [114]

"Dementia and its first or transitional stage, mild cognitive impairment (MCI), is a major concern for the aging Japanese society. Thus, the use of dietary supplements to improve or maintain cognitive function has become a topic of public interest. Objective: In this study, we evaluated the effects of a composite supplement containing food-derived antioxidants, specifically astaxanthin and sesamin (AS), on cognitive function in people with MCI. Method: Twenty-one healthy participants with MCI were recruited in our double-blind placebo-controlled pilot study. They were assigned to either an AS group, who received ingestible capsules containing AS, or a placebo group, who received identical placebo capsules. To assess cognitive functions, we performed the Japanese version of the Central Nervous System Vital Signs (CNSVS) test and the Alzheimer's Disease Assessment Scale-Cog test at baseline, after 6 weeks, and after 12 weeks of dietary supplementation. Results: The CNSVS test revealed significant improvements in psychomotor speed and processing speed in the AS group compared with the placebo group, suggesting that the daily supplementation of AS improved cognitive functions related to the ability to comprehend, and perform complex tasks quickly and accurately. Conclusion: Our results provide support for the use of AS as a dietary supplementation for improving cognitive functions.

Francesca Crosta et al. (2020). "Improvement of Executive Function after Short-Term Administration of an Antioxidants Mix Containing Bacopa, Lycopene, Astaxanthin and Vitamin B12: The BLAtwelve Study." Nutrients. 2020 Dec 27;13(1):56. [101]

"During the last few years increasing interest has been focused on antioxidants as potentially useful agents in the prevention of the onset and progression of cognitive dysfunction. In this randomized, double-blind, controlled, parallel arm study, the effects of daily consumption of an antioxidant mix on cognitive function in healthy older adults were evaluated. After a 1 week run-in period, 80 subjects aged 60 years or more, and with no evidence of cognitive dysfunction, were randomly allocated to a mix of four bioactive compounds (bacopa, lycopene, astaxanthin, and vitamin B12) or matched placebo, taken orally once a day for 8 weeks. The primary objective of the study was to evaluate the changes in trial making test (TMT) scores from

baseline to 8 weeks of treatment, analyzed in the following hierarchical order: TMT-B, TMT-A, and TMT-B minus TMT-A. TMT-B increased in the control group (+3.46 s) and decreased in the active group (-17.63 s). The treatment difference was -21.01 s in favor of the active group (95% C.I. -26.80 to -15.2, $p < 0.0001$). The decrease in TMT-A was significantly higher in the active group (-6.86 s) than in the control group (-0.37 s). TMT-B minus TMT-A increased in the control group (+3.84 s) and decreased in the active group (-10.46 s). The increase in letter fluency in the verbal fluency test (VFT) was also significantly higher in the active group and statistically significant (+5.28 vs. +1.07 words; $p < 0.001$). Our findings provide encouraging evidence that regular dietary supplementation with bacopa, lycopene, astaxanthin, and vitamin B12 may be an effective dietary approach for counteracting cognitive changes associated with brain aging."

Jose-Manuel Carrascosa et al. (2017). "Increase in minimal erythemal dose following oral administration of an antioxidant complex based on a mix of carotenoids: Double-blind, placebo-controlled trial." Photodermatol Photoimmunol Photomed. 2017 Sep;33(5):284-286. [102]

"The primary objective of this study was to assess the effect of oral administration of a combination of antioxidants on acute tolerance to solar radiation as measured by changes in minimal erythema dose (MED) 28 and 56 days after start of treatment. This was a prospective, double-blind, placebo-controlled trial carried out in a single center. The participants were 43 healthy volunteers aged between 18 and 60 years whose skin phototype was either II (at least 60% of participants) or III. The study was approved by a local ethical committee (EVIC Hispania; resolution CI-S08/14 February 2014), and all patients signed an informed consent. Exclusion criteria included: personal history of hypersensitivity to sunlight, phototoxicity and/or photoallergy; current therapy with potential phototoxic/photoallergic drugs; exposure to sunlight 4 weeks before the study; phototypes I and from IV to VI; intention to receive natural or artificial sunlight during the study; previous history of melanoma and the intake of any nutritional supplement that could interfere with the clinical results 4 weeks before. Participants were assigned to two groups and received either the active formulation or a placebo (a pill devoid of the active ingredient but identical in all other respects to the trial product). The regimen was 1 tablet daily in the morning with breakfast for 56 days (±3 days). The active formulation (Genosun oral®) contained a combination of astaxanthin (4 mg), β-carotene (4.8 mg), vitamin E (6 mg), vitamin C (40 mg), lutein (2.4 mg) and lycopene (2.4 mg). The protective effect of this formulation on skin exposed to erythemal UVR was assessed by measuring MED at baseline (before taking the first dose) and after 28 and 56 days of treatment (D1, D29, D57). In summary, the combination product tested has a protective effect against erythemal radiation. However, based on the findings of this study, the increase in the MED value is modest. Thus, its use should be supplemental to other strategies of topical - that is, broad spectrum sunscreens - and physical photoprotection - that is, clothing or hats."

Divya Birudaraju et al. (2020). "A combined effect of Cavacurcumin, Eicosapentaenoic acid (Omega-3s), Astaxanthin and Gamma -linoleic acid (Omega-6) (CEAG) in healthy volunteers- a randomized, double-blind, placebo-controlled study." Clin Nutr ESPEN. 2020 Feb;35:174-179. [103]

"Inflammation plays a key role and is one of the early steps in the pathogenesis of endothelial function, thereby increasing the risk of hypertension (HTN), coronary artery disease (CAD), stroke and several other risk factors of cardiovascular disease (CVD). We assessed the efficacy for improving cardiovascular health (blood pressure, inflammation and endothelial reactivity) over a 4-week intervention period in healthy individuals. Methods: We performed a randomized, double-blinded, placebo-controlled, randomized clinical trial to investigate Curcumin, Eicosapentaenoic acid (EPA), Astaxanthin and Gamma -linoleic acid (GLA) (CEAG) supplements with 80 individuals (30 men and 50 women). The mean age of participants was 48.8 ± 16.0 years. Participants were enrolled and randomized to active or placebo and followed for 4 weeks. Paired and Independent T-tests were used to analyze the mean differences between and within groups. Results: The primary endpoints of the study were the effect on inflammatory markers (IL-6, CRP), endothelial function and blood pressure at 4 weeks. There was a significant reduction in mean SBP at 4 weeks in the CEAG group compared to placebo [mean ± SD 4.7 ± 6.8 (p = 0.002)]. Relative to placebo, active group showed a significant decrease in High sensitivity C Reactive Protein (hsCRP) (-0.49 ± 1.9 vs + 0.51 ± 2.5, p = 0.059) and blunted increase in IL-6 (+0.2 vs + 0.4 in placebo, p = 0.60). Conclusion: Inflammatory markers were reduced or blunted by CEAG, with a robust increase in both EPA levels and the fatty acid index. Furthermore, systolic BP was reduced over 4 weeks with concurrent improvement in endothelial function."

J Atilio Canas et al. (2017). "Effects of Mixed Carotenoids on Adipokines and Abdominal Adiposity in Children: A Pilot Study." J Clin Endocrinol Metab. 2017 Jun 1;102(6):1983-1990. [104]

"Carotenoids have been implicated in the regulation of adipocyte metabolism. Objective: To compare the effects of mixed-carotenoid supplementation (MCS) versus placebo on adipokines and the accrual of abdominal adiposity in children with obesity. Design and setting: Randomized (1:1), double-blind, placebo-controlled intervention trial to evaluate the effects of MCS over 6 months in a subspecialty clinic. Participants: Twenty (6 male and 14 female) children with simple obesity [body mass index (BMI) > 90%], a mean age (± standard deviation) of 10.5 ± 0.4 years, and Tanner stage I to V were enrolled; 17 participants completed the trial. Intervention: MCS (which contains β-carotene, α-carotene, lutein, zeaxanthin, lycopene, astaxanthin, and γ-tocopherol) or placebo was administered daily. Main outcome measures: Primary outcomes were change in β-carotene, abdominal fat accrual (according to magnetic resonance imaging), and BMI z-score; secondary outcomes were adipokines and markers of insulin resistance. Results: Cross-sectional analysis of β-carotene showed inverse correlation with BMI z-score, waist-to-height ratio, visceral adipose tissue, and subcutaneous adipose tissue (SAT) at baseline. MCS increased β-carotene, total adiponectin, and high-molecular-weight adiponectin compared with placebo. MCS led to a greater reduction in BMI z-score, waist-to-height ratio, and SAT compared with placebo. The percentage change in β-carotene directly correlated with the percentage change in SAT. Conclusions: The decrease in BMI z-score, waist-to-height ratio, and SAT and the concomitant increase in the concentration of β-carotene and high-molecular-weight adiponectin by MCS suggest the putative beneficial role of MCS in children with obesity."

Keiko Kono et al. (2014). "Effect of Multiple Dietary Supplement Containing Lutein, Astaxanthin, Cyanidin-3-Glucoside, and DHA on Accommodative Ability." Curr Med Chem. 2014 Aug; 14(2): 114–125. [77]

"The study aimed to verify that ingestion of multiple dietary supplement containing lutein, astaxanthin, cyanidin-3-glucoside and docosahexaenoic acid (DHA) would improve accommodative ability of aged and older subjects who were aware of eye strain on a daily basis. Methods: A randomized double-blind placebo-controlled parallel group comparison study was conducted for 48 participants aged 45 to 64 years who complained of eye strain. The subjects took multiple dietary supplement containing 10 mg of lutein, 20 mg of bilberry extract and 26.5 mg of black soybean hull extract (a total of 2.3 mg of cyanidin-3-glucoside in both extracts), 4 mg of astaxanthin, and 50 mg of DHA (test supplement) or placebo for four consecutive weeks. Near-point accommodation (NPA) and subjective symptoms were evaluated both before and after four weeks' intake. Results: The variation of the NPA of both eyes from baseline to 4 weeks' post-intake in the test supplement group was significantly higher than in the placebo group (1.321±0.394 diopter (D) in the test supplement group and 0.108±0.336 D in the placebo group, $p=0.023$). The multiple dietary supplement group showed improvement in the NPA. Regarding subjective symptoms, significant improvement of "stiff shoulders or neck" and "blurred vision" was also found in the test supplement group compared to the placebo group ($p<0.05$). There were no safety concerns in this study. Conclusion: This study shows that multiple dietary supplement containing lutein, astaxanthin, cyanidin-3-glucoside, and DHA has effect to improve accommodative ability and subjective symptoms related to eye fatigue."

Astaxanthin in Food Applications

Natural astaxanthin is a bioactive compound whose anti-oxidative activity and health-promoting properties, resulting from its unique structure, have been well-documented. However, due to its high price and limited sources, it is poorly known to food consumers and underestimated by food producers. For this reason, it is necessary to spread information about this pigment. The anti-oxidative potential of astaxanthin as well as its coloring properties enable food technologists to design a sensorily attractive assortment of functional foods and active packages [112].

Food technologists are able to create a variety of functional foods and active packages that are sensorily appealing, thanks to the coloring properties and anti-oxidative potential of astaxanthin.

Francesco Landi et al. (2019). "Effects of a New Combination of Medical Food on Endothelial Function and Lipid Profile in Dyslipidemic Subjects: A Pilot Randomized Trial." Biomed Res Int. 2019 Jan 6;2019:1970878. [113]

"Nutritional approaches to improve dyslipidemias have been recently developed, but evidences on different medical foods are often incomplete. The main aim of our study was to evaluate the effects on endothelial function, lipid profile, and glucose metabolism of two different combinations of nutraceuticals, first one containing Bergavit (200 mg Citrus bergamia), Omega-3 (400 mg), Crominex 3+ (10 mcg trivalent chromium), and red yeast rice (100 mg; 5 mg monacolin K) and second one containing red yeast rice (200 mg; 3 mg monacolin K), Berberine (500 mg), Astaxanthin (0.5 mg), folic acid (200 mcg), Coenzyme Q10 (2 mg), and Policosanol (10 mg). Fifty subjects affected by dyslipidemia not requiring statin treatment were enrolled in this randomized, blind, controlled trial and submitted to blood sampling for lipid and glucose profiles and instrumental evaluation of endothelial function before and after 6 weeks of treatment with nutraceuticals. Both nutraceutical combinations improved the lipid profile; the nutraceutical containing 5 mg of monacolin K, 200 mg of the extract Citrus bergamia, 400 mg of Omega-3, and 10 mcg of trivalent chromium entailed a significant improvement of endothelial function with enhanced cholesterol lowering effect. In conclusion, this study confirms the positive effect of functional food on lipid profile and endothelial function in absence of major undesirable effects."

I.M. Petyaev et al. (2018). "Markers of Hypoxia and Oxidative Stress in Aging Volunteers Ingesting Lycosomal Formulation of Dark Chocolate Containing Astaxanthin." J Nutr Health Aging. 2018;22(9):1092-1098. [105]

"To determine if ingestion of lycosome-formulated dark chocolate (DC) containing astaxanthin (ASTX) improves bioavailability of ASTX and affects markers of hypoxia and oxidative stress in aging individuals. Design: Randomized, blinded, four-arm, prospective study. Settings: Lycotec Ltd, Cambridge, United Kingdom and Institute of Cardiology, Saratov, Russian Federation. Participants: 32 healthy individuals aged 60-70 years with confirmed signs of oxidative stress (increased serum levels of oxidized LDL and malonic dialdehyde) randomized into four study groups (8 volunteers each). Intervention: Volunteers of first group were given orally 10 gr of dark chocolate (DC). Individuals from the second group received 7 mg of astaxanthin (ASTX). Third group of volunteers was supplemented with 10 gr of DC and 7 mg of ASTX ingested simultaneously as two separate formulations. Last group of the individuals was given 10 gr of a lycosomal formulation of DC containing 7 mg of co-crystalized ASTX (L-DC-ASTX), a newly developed highly bioavailable nutraceutical composition of DC containing 2 groups of antioxidants (cocoa flavanols and ASTX). All formulations were given orally, once daily for a month. Measurements: Serum ASTX was measured by high-performance liquid chromatography. Nitric oxide, malonic dialdehyde and oxidized LDL were quantified spectrophotometrically. Oxygenation parameters were evaluated by near-infrared spectroscopy. Results: One month ingestion of singular formulation of ASTX lead to a 20 fold buildup in serum ASTX level whereas the 4 week ingestion of L-DC-ASTX formulation was accompanied by more prominent accumulation of ASTX in serum (a 40 fold increase over the basal values) at the same daily dose of ASTX. Both antioxidants taken separately decreased serum levels of oxidized LDL and malonic dialdehyde. However effect of L-DC-

ASTX formulation was more prominent. ASTX ingested alone caused a borderline increase (p=0.054) in serum nitric oxide (NO) levels, whereas DC ingestion lead to small but statistically significant increase in serum NO concentration. Higher values of NO level were seen after co-ingestion of DC and ASTX, especially in case of L-DC-ASTX formulation suggesting additive/synergistic effects of DC and ASTX on nitric oxide production. These changes were in agreement with the increase in plasma oxygen transport and tissue oxygen saturation seen in the volunteers supplemented with L-DC-ASTX formulation. Conclusion: The nutraceutical formulation of DC and ASTX with an enhanced bioavailability of ASTX can be efficiently used for the correction of oxidative status in aging individuals."

Hitomi Saito et al. (2017). "Zinc-rich oysters as well as zinc-yeast- and astaxanthin-enriched food improved sleep efficiency and sleep onset in a randomized controlled trial of healthy individuals." Mol Nutr Food Res. 2017 May;61(5). [106]

Zinc is an essential mineral that plays an important role in the body. We previously reported that orally feeding zinc-enriched yeast to mice induces nonrapid-eye-movement sleep. In addition, astaxanthin, an antioxidant abundant in seafood such as salmon and krill, is able to chelate minerals and may promote zinc absorption, which in return may also improve sleep. The purpose of our study was to examine the effect of zinc-rich and astaxanthin-containing food on sleep in humans. Methods and results We conducted a randomized, double-blinded, placebo-controlled parallel group trial of 120 healthy subjects and recorded their night activity by actigraphy for 12 weeks. These subjects were divided into four groups: placebo, zinc-rich food, zinc-, and astaxanthin-rich food, and placebo supplemented with zinc-enriched yeast and astaxanthin oil. Compared with the placebo group, the zinc-rich food group efficiently decreased the time necessary to fall asleep and improved sleep efficiency, whereas the group that ingested zinc-enriched yeast and astaxanthin oil significantly improved the sleep onset latency. Conclusion: Actigraphic sleep monitoring demonstrated that eating zinc-rich food improved sleep onset latency as well as improved the sleep efficiency in healthy individuals.

K.C. Maki at 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 2015 Aug;99:41-6. [107]

"This randomized, double-blind, placebo-controlled multi-center trial investigated the lipid-altering effects of a medical food (PDL-0101) providing 1.8 g/d eicosapentaenoic acid; 12 mg/d astaxanthin, a marine algae-derived carotenoid; and 100 mg/d tocopherol-free gamma/delta tocotrienols enriched with geranylgeraniol, extracted from annatto, on triacylglycerols (TAG), other lipoprotein lipids, and oxidized low-density lipoprotein (LDL) in 102 subjects with TAG 150-499 mg/dL (1.69-5.63 mmol/L) and LDL cholesterol (LDL-C) ≥70 mg/dL (1.81 mmol/L). Compared to placebo, after eight weeks of treatment, PDL-0101 significantly reduced median TAG (-9.5% vs. 10.6%, p<0.001), while not significantly altering mean LDL-C (-3.0% vs. -8.0% for PDL-0101 and placebo, respectively, p=0.071), mean high-density lipoprotein cholesterol (~3% decrease in both groups, p=0.732), or median oxidized LDL concentrations (5% vs. -5% for PDL-0101 and placebo, respectively, p=0.112). These results demonstrate that PDL-0101 is an effective medical food for the management of elevated TAG."

Additional Studies

Main conclusions

Izzo et al. (2010). "Effects of nutraceuticals on prevalence of metabolic syndrome and on calculated Framingham Risk Score in individuals with dyslipidemia." J Hypertens, 2010. 28(7): p. 1482-7. [108]

In a large clinical sample of patients with moderate cardiovascular risk, combination of NUT with dietary counseling reduces central obesity, improves lipid profile, diastolic BP and FRS, and decreases prevalence of MetS.

G Belcaro et al. (2010). "MF Afragil® in the treatment of 34 menopause symptoms: a pilot study." Panminerva Med. 2010 Jun;52(2 Suppl 1):49-54. [109]

Following the treatment with combinatorial supplement with astaxanthin, the total MSSQ score (Common Symptoms, Changes and Pains) was reduced by more than 45%. There was a significant reduction in hot flashes, CNS symptoms (depression, anxiety and panic disorders), incontinence and joint pain, which are among the most frequent symptoms of climacteric status.

Balcerczyk, A.G. et al.(2014). "Enhanced antioxidant capacity and anti-ageing biomarkers after diet micronutrient supplementation." Molecules, 2014. 19(9): p. 14794-808. [90]

This study focuses on the influence of a diet supplement, NucleVital®Q10 Complex, on parameters related to redox homeostasis and ageing. Our results demonstrate beneficial effects concerning the antioxidant potential of plasma as well as biomarkers related to ageing even after short term supplementation of diet with NucleVital®Q10 Complex.

Iwasaki, T. et al. (2006). "Effects of Astaxanthin on Eyestrain Induced by Accommodative Dysfunction." Journal of the Eye, 2006. 23(6): p. 826-834. Cyanotech corporation. [71]

The symptoms eye fatigue, eye heaviness, blurred vision and eye dryness in P group were increased, but Ax group showed increased in eye fatigue and eye heaviness. On the basis of these results, we concluded that astaxanthin has the effects of reducing and preventing eyestrain induced by accommodative dysfunction.

Nakamura A. et al. (2004). "Changes in visual function following peroral astaxanthin." Japanese Journal of Clinical Ophthalmology, 2004. 58(6): p. 1051-1054. [70]

After ingestion of astaxanthin for consecutive 28 days, the uncorrected far visual acuity significantly improved in groups receiving 4 mg or 12 mg. The accommodation time significantly shortened in groups receiving 4 mg or 12 mg. There was no change in refraction, flicker fusion frequency, or pupillary reflex.

F. H. Comhaire et al. (2005). "Combined conventional/antioxidant "Astaxanthin" treatment for male infertility: a double blind, randomized trial." Clinical Trial Asian J Androl. 2005 Sep;7(3):257-62. [110]

Although the present study suggests a positive effect of Astaxanthin on sperm parameters and fertility, the results need to be confirmed in a larger trial before recommending Astaxanthin for the complementary treatment of infertile men.

Spiller et al.(2006). "Effect of daily use of natural astaxanthin on symptoms associated with tennis elbow (lateral humeral epicondylitis)", 2006. [111]

The group receiving astaxanthin had a significant increase in grip strength measurements when compared to the group receiving the placebo.

TAKAHASHI NANAKO et al. (2005). "Effects of Astaxanthin on Accommodative Recovery" Journal of Clinical Therapeutics & Medicines), Vol.21, Issue 4, 431-436. Cyanotech corporation .[72]

We have examined the effects of AX on accommodative recovery from rest after operation. Ten healthy volunteers participated in the study. One subject was removed from the study as that person developed allergic conjunctivitis during the study. Therefore, only nine volunteers were evaluated (9 dominant eyes) based the objective diopter value, the HFC value, and the accommodative reaction value. The result showed the HFC value after operation decreased significantly after AX intake compared to that of before uptake. This study suggested that AX had effect on accommodation and worked on accommodative fatigue during the recovery process, which aided in relieving fatigue rapidly.

Conclusion

The document represents a synopsis of clinical research on natural astaxanthin in humans. 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. The current data indicate that astaxanthin is a valuable functional ingredient with applications for skin health, anti-aging, muscle endurance/recovery and cardiovascular health. Due to its wide range of benefits astaxanthin is getting more popular in combinatorial applications in food and food supplements.

Dietary supplements and functional food 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 wellbeing, and offers exciting opportunities for the nutraceutical industry.

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Head office, Sales and Cultivation Facility in Iceland

Algalif Iceland ehf.
Bogatrod 10
262 Reykjanesbaer
Iceland

Website

www.algalif.com

Contact info

Tel: +354-571-1066
sales@algalif.com
info@algalif.com

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