

# The Medical Research of Astaxanthin Eye Health

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# Introduction

The body of medical research on Astaxanthin is fast approaching critical mass for several diverse applications. Over the last decade in particular, the amount of studies done by private researchers and universities throughout the world has escalated. The intense interest in undertaking new research on Astaxanthin is a direct result of the remarkable qualities of this fascinating molecule.

Cyanotech Corporation\* feels that it is important to have a library of this research available for interested persons; hence we have created this document. Below the reader will find selected research abstracts on the health benefits of Astaxanthin. It was not practical to include full studies due to the substantial amount of literature available; however, with these abstracts, the reader will obtain a working knowledge of potential applications for Astaxanthin in human nutrition. The abstracts are presented according to health benefit as noted in the table of contents. In the case of studies that focused on more than one health benefit, the study is categorized according to the primary area of research within the abstract.

Any questions may be directed to Cyanotech Corporation, Kailua-Kona, Hawaii, USA, by e-mail at [info@cyanotech.com](mailto:info@cyanotech.com) or by telephone at 808.326.1353.

\* Cyanotech Corporation is the world leader in microalgae technology. Cyanotech produces BioAstin Natural Astaxanthin at its 90 acre (40 hectare) microalgae farm on Hawaii's pristine Kona Coast.

Japanese Journal of Clinical Ophthalmology VOL.58;NO.6;PAGE.1051-1054(2004)

**Changes in visual function following peroral astaxanthin**

NAKAMURA AKIRA; ISOBE RYOKO; OTAKA YASUHIRO; ABEMATSU YASUKO;  
NAKATA DAISUKE; HONMA CHIKA ; SAKURAI SHIZUKA; SHIMADA YOSHIAKI;  
HORIGUCHI MASAYUKI

We evaluated the effect of astaxanthin on visual function in 49 eyes of 49 healthy volunteers. They were over 40 years of age. They were divided into 4 groups matched for age and gender. Each group was given peroral astaxanthin once a day. The dosage was 0mg, 2mg, 4mg, or 12mg for each group. After ingestion of astaxanthin for consecutive 28 days, the uncorrected far visual acuity significantly improved in groups receiving 4mg or 12mg. The accommodation time significantly shortened in groups receiving 4mg or 12mg. There was no change in refraction, flicker fusion frequency, or pupillary reflex.

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**The supplementation effect of Astaxanthin on Accommodation and Asthenopia**

NAGAKI YASUNORI; MIHARA MIHARU; TSUKAHARA HIROKI; ONO SHIGEAKI

This double blind randomized placebo controlled study examined the supplementation effects of Haematococcus (H) pluvialis derived astaxanthin on subjects suffering from visual display terminal (VDT) induced visual fatigue. Subjects were divided into two groups: 6 mg astaxanthin treated and placebo groups. Furthermore, the safety of astaxanthin intake was simultaneously assessed. After the 4 week supplementation period, the groups' visual accommodation was evaluated as well as a subjective questionnaire designed to evaluate visual asthenopia (eye fatigue). Twenty five subjects of the astaxanthin treated group and 23 subjects of the placebo group were examined for eye fatigue. For safety evaluation, 31 treated subjects and 28 placebo subjects were analysed. We report the following observations: 1. In the astaxanthin treated group, the change of accommodation before and after supplementation significantly improved compared with the placebo group. 2. The astaxanthin supplemented group exhibited a significant rate of change in the accommodation compared with the placebo group. 3. The subjective questionnaire evaluating visual asthenopia revealed a marked reduction in "heavy head" claims. Other typical improvements of fatigue symptoms included "dimness of sight" and "stiff shoulders and back". 4. No significant differences were detected between the treatment and the placebo groups after 4 weeks of supplementation in the safety parameters analyzed, and adverse event. These results suggest that 6 mg of astaxanthin per day from a H. pluvialis algal extract can improve eye fatigue. Moreover, astaxanthin can be safely consumed at this level by healthy adults.

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**Effect of Astaxanthin on Accommodation and Asthenopia-Efficacy-Identification Study in Healthy Volunteers-**

SHIRATORI KENJI; OGAMI KAZUHIRO; NITTA TAKUYA; SHINMEI YASUHIRO; CHIN SHINKI; YOSHIDA KAZUHIKO; TSUKAHARA HIROKI; TAKEHARA ISAO; ONO SHIGEAKI

A double-blind study was conducted to confirm the efficacy of *H. pluvialis* Astaxanthin on accommodation and asthenopia and its safety. Two groups of subjects were compared, wherein one was given 0mg of Astaxanthin (as a control group) and the other was given 6mg of Astaxanthin (AX group). The subjects were healthy volunteers who complained of asthenopia. Twenty were enrolled in each group, and the testing food was administered during 4 weeks. Sub-objective accommodation power, positive accommodation time and negative accommodation time were measured before and after administration to objectively evaluate the degree of asthenopia. Additionally, subjective degree of asthenopia by volunteers was evaluated using VAS. The safety was assessed by changes in value of laboratory tests between pre- and post-administrations and by the doctor's questions. 1) Sub-objective accommodation power (rate of change) of the AX group was significantly higher than that of the control group. 2) The AX group showed significantly higher rate of positive and negative accommodation times (rate of change) compared to those of the control group. 3) In the AX group, subjective degree of asthenopia measured by VAS showed significant improvement in two parameters, i.e., "blar-eye feeling" and "tendency of irritation" than the control group. 4) No changes in laboratory tests of clinically controversial were noted and also no adverse events suggesting causal relationship with the testing food were found. In conclusion, administration of 6mg/day (in a daily dosage of 2 capsules; 3mg/capsule) of *H. pluvialis* Astaxanthin improved accommodation power and subjective symptoms of asthenopia. Also, Astaxanthin was confirmed to be completely safe.

Eye Health105

J Pharm Pharmacol. 2008 Oct;60(10):1365-74.

**Astaxanthin, a dietary carotenoid, protects retinal cells against oxidative stress**

**in-vitro and in mice in-vivo.** Nakajima Y, Inokuchi Y, Shimazawa M, Otsubo K, Ishibashi T, Hara H. Department of Biofunctional Evaluation, Molecular Pharmacology, Gifu Pharmaceutical University, 5-6-1 Mitahora-higashi, Gifu 502-8585, Japan. We have investigated whether astaxanthin exerted neuroprotective effects in retinal ganglion cells in-vitro and in-vivo. In-vitro, retinal damage was induced by 24-h hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>) exposure or serum deprivation, and cell viability was measured using a WST assay. In cultured retinal ganglion cells (RGC-5, a rat ganglion cell-line transformed using E1A virus), astaxanthin inhibited the neurotoxicity induced by H<sub>2</sub>O<sub>2</sub> or serum deprivation, and reduced the intracellular oxidation induced by various reactive oxygen species (ROS). Furthermore, astaxanthin decreased the radical generation induced by serum deprivation in RGC-5. In mice in-vivo, astaxanthin (100 mg kg<sup>-1</sup>), p.o., four times) reduced the retinal damage (a decrease in retinal ganglion cells and in thickness of inner plexiform layer) induced by intravitreal N-methyl-D-aspartate (NMDA) injection. Furthermore, astaxanthin reduced the expressions of 4-hydroxy-2-nonenal (4-HNE)-modified protein (indicator of lipid peroxidation) and 8-hydroxy-deoxyguanosine (8-OHdG; indicator of oxidative DNA damage). These findings indicated that astaxanthin had neuroprotective effects against retinal damage in-vitro and in-vivo, and that its protective effects may have been partly mediated via its antioxidant effects. PMID: 18812030 [PubMed - indexed for MEDLINE]

Eye Health106

Invest Ophthalmol Vis Sci. 2008 Apr;49(4):1679-85.

**Inhibition of choroidal neovascularization with an anti-inflammatory carotenoid astaxanthin.** Izumi-Nagai K, Nagai N, Ohgami K, Satofuka S, Ozawa Y, Tsubota K, Ohno S, Oike Y, Ishida S.

Laboratory of Retinal Cell Biology, Keio University of Medicine, Tokyo, Japan.

**PURPOSE:** Astaxanthin (AST) is a carotenoid found in marine animals and vegetables. The purpose of the present study was to investigate the effect of AST on the development of experimental choroidal neovascularization (CNV) with underlying cellular and molecular mechanisms.

**METHODS:** Laser photocoagulation was used to induce CNV in C57BL/6J mice. Mice were pretreated with intraperitoneal injections of AST daily for 3 days before photocoagulation, and treatments were continued daily until the end of the study. CNV response was analyzed by volumetric measurements 1 week after laser injury. Retinal pigment epithelium-choroid levels of IkappaB-alpha, intercellular adhesion molecule (ICAM)-1, monocyte chemoattractant protein (MCP)-1, interleukin (IL)-6, vascular endothelial growth factor (VEGF), VEGF receptor (VEGFR)-1, and VEGFR-2 were examined by Western blotting or ELISA. AST was applied to capillary endothelial (b-End3) cells, macrophages, and RPE cells to analyze the activation of NF-kappaB and the expression of inflammatory molecules. **RESULTS:** The index of CNV volume was significantly suppressed by treatment with AST compared with that in vehicle-treated animals. AST treatment led to significant inhibition of macrophage infiltration into CNV and of the in vivo and in vitro expression of inflammation-related molecules, including VEGF, IL-6, ICAM-1, MCP-1, VEGFR-1, and VEGFR-2. Importantly, AST suppressed the activation of the NF-kappaB pathway, including IkappaB-alpha degradation and p65 nuclear translocation. **CONCLUSIONS:** AST treatment, together with inflammatory processes including NF-kappaB activation, subsequent upregulation of inflammatory molecules, and macrophage infiltration, led to significant suppression of CNV development. The present study suggests the possibility of AST supplementation as a therapeutic strategy to suppress CNV associated with AMD. Publication Types:

PMID: 18385091 [PubMed - indexed for MEDLINE]

Eye Health107

Nippon Ganka Gakkai Zasshi. 2009 Mar;113(3):403-22; discussion 423.

**[Lifestyle-related diseases and anti-aging ophthalmology: suppression of retinal and choroidal pathologies by inhibiting renin-angiotensin system and inflammation]** [Article in Japanese]

**Ishida S.** Inaida Endowed Department of Anti-Aging Ophthalmology, Laboratory of Retinal Cell Biology, Center for Integrated Medical Research, Keio University School of Medicine, Tokyo, Japan. [ishidasu@sc.itc.keio.ac.jp](mailto:ishidasu@sc.itc.keio.ac.jp) Lifestyle-related diseases cause macro-and microangiopathies in the major organs including the brain, heart, kidney, and eye, and as a result, shorten the lifespan. The renin-angiotensin system (RAS) has recently been shown to contribute to the processes of accelerated aging caused by lifestyle-related diseases from visceral obesity in the early stage to late-onset organ damage. Vision-threatening diabetic retinopathy and age-related macular degeneration (AMD), associated with lifestyle-related diseases as risk factors for progression, develop retinal and choroidal neovascularization (CNV), respectively, in their advanced stages. We have found that tissue RAS is activated in the pathogenesis of diabetic retinopathy and CNV, leading to angiotensin type 1 receptor(AT1-R)-mediated expression of inflammation-related molecules including vascular endothelial growth factor (VEGF), intercellular adhesion molecule (ICAM)-1, and monocyte chemotactic protein(MCP)-1. Neuronal dysfunction in diabetic retinopathy is also shown to result from AT1-R-mediated degradation of synaptic proteins. Moreover, we revealed for the first time that the receptor for prorenin [(pro) renin receptor] is expressed in the eye, although prorenin was until recently believed to be just an inactive precursor of renin. Prorenin binds to the receptor that causes dual activation of its intracellular signaling and tissue RAS, and this pathogenic mechanism is termed receptor-associated prorenin system (RAPS)'. We have demonstrated the contribution of RAPS to the pathogenesis of CNV and dual regulation of VEGF and MCP-1 by signal transduction via (pro) renin receptor and AT1-R. Next, we report the potential validity of food factor supplements as a therapeutic strategy for preventing the retinal and choroidal pathologies driven by RAS-induced inflammatory and angiogenic molecules. Functional food factors examined include lutein in yellow-green vegetables, the omega-3 polyunsaturated fatty acid eicosapentaenoic acid purified from fish oil, and red pigment astaxanthin from salmon and shrimp. We recently revealed that these food factors prevent intraocular angiogenesis and inflammation by inhibiting the expression of inflammatory molecules including VEGF, ICAM-1, and MCP-1. Preventive medicine for AMD and diabetic retinopathy, both of which have lifestyle-related diseases as a systemic background, has attracted growing attention. In the present review, we provide biological evidence for RAS inhibition and food factor supplementation in the early intervention for retinal and choroidal pathologies as an 'anti-aging ophthalmology' approach.

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Chem Res Toxicol. 2009 Feb 4. [Epub ahead of print]

**Astaxanthin Interacts with Selenite and Attenuates Selenite-Induced**

**Cataractogenesis.** Liao JH, Chen CS, Maher TJ, Liu CY, Lin MH, Wu TH, Wu SH. Institute of Biological Chemistry, Academia Sinica, Taipei 115, Taiwan, Department of Pharmaceutical Sciences, Massachusetts College of Pharmacy and Health Sciences, Boston, Massachusetts 02115, USA, and School of Pharmacy, College of Pharmacy, Taipei Medical University, Taipei 110, Taiwan. Selenite, the most commonly encountered toxic form of selenium, in overdose, is used to induce cataracts in rats. This study demonstrated that selenite, but not selenate, would interact with the carotenoid astaxanthin (ASTX), as determined using isothermal titration calorimetry and NMR. The maximum absorption of ASTX decreased with increasing selenite concentration, indicating that the conjugated system of ASTX was changed by selenite. Such interactions between ASTX and selenite were also supported by the attenuation of selenite-induced turbidity by ASTX (0-12.5  $\mu$ M) in vitro. In vivo experiments also showed that ASTX attenuated selenite-induced cataractogenesis in rats. In summary, this is the first report of a direct interaction of ASTX with selenite. This interaction is supported by an in vitro assay and may be partially responsible for the ASTX observed in vivo protection against selenite-induced cataractogenesis. PMID: 19193053 [PubMed - as supplied by publisher]

Eye Health109

Ophthalmology. 2008 Feb;115(2):324-333.e2. Epub 2007 Aug 22.

**Carotenoids and antioxidants in age-related maculopathy italian study: multifocal electroretinogram modifications after 1 year.** Parisi V, Tedeschi M, Gallinaro G, Varano M, Saviano S, Piermarocchi S; CARMIS Study Group. Fondazione G. B. Bietti-Istituto di Ricovero e Cura a Carattere Scientifico, Roma, Italy. vparisi@tin.it OBJECTIVE: 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  $\geq$  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 $\pm$ 4.31 years; 15 eyes); 12 patients had no dietary supplementation during the same period (nontreated AMD [NT-AMD] group; mean age, 69.7 $\pm$ 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. PMID: 17716735 [PubMed - indexed for MEDLINE]

Eye Health110

J Photochem Photobiol B. 2007 Jul 27;88(1):1-10. Epub 2007 May 1.

**Lutein, zeaxanthin and astaxanthin protect against DNA damage in SK-N-SH human neuroblastoma cells induced by reactive nitrogen species. Santocono M, Zurria M, Berrettini M, Fedeli D, Falcioni G.**

Medical Department, SIFI SpA, Via E. Patti 36, Lavinaio (CT), Italy. The purpose of this study was to evaluate the ability of the predominant carotenoids (lutein and zeaxanthin) of the macular pigment of the human retina, to protect SK-N-SH human neuroblastoma cells against DNA damage induced by different RNOS donors. Although astaxanthin has never been isolated from the human eye, it was included in this study because its structure is very close to that of lutein and zeaxanthin and because it affords protection from UV-light. DNA damage was induced by GSNO-MEE, a nitric oxide donor, by Na(2)N(2)O(3), a nitroxyl anion donor and by SIN-1, a peroxynitrite-generating agent. DNA damage was assessed using the comet assay, a rapid and sensitive single cell gel electrophoresis technique able to detect primary DNA damage in individual cells. The tail moment parameter was used as an index of DNA damage. The values of tail moment increased in all the samples incubated with the RNOS donors, indicating DNA impairment. Data obtained show that the ability of zeaxanthin, lutein, and astaxanthin to reduce the DNA damage depends on the type of RNOS donor and the carotenoid concentration used. All the carotenoids studied were capable of protecting against DNA damage in neuroblastoma cells when the cells were exposed to GSNO-MEE. However, a different behaviour was present when the other two RNOS donors were used. The presence of a carotenoid alone (without an RNOS donor) did not cause DNA damage. Spectrophotometric studies showed that the order with which tested carotenoids reacted with RNOS was not always in agreement with the DNA protection results. The data from this study provides additional information on the activities of the macular pigment carotenoids of the human retina. Publication Types:

PMID: 17548202 [PubMed - indexed for MEDLINE]

Eye Health111

J Agric Food Chem. 2006 Mar 22;54(6):2418-23.

**Astaxanthin protects against oxidative stress and calcium-induced porcine lens protein degradation.** Wu TH, Liao JH, Hou WC, Huang FY, Maher TJ, Hu CC. Department

of Clinical Pharmacy, School of Pharmacy, Taipei Medical University, Taipei 110, Taiwan.

thwu@tmu.edu.tw Astaxanthin (ASTX), a carotenoid with potent antioxidant properties, exists naturally in various plants, algae, and seafoods. In this study, we investigated the in vitro ability of ASTX to protect porcine lens crystallins from oxidative damage by iron-mediated hydroxyl radicals or by calcium ion-activated protease (calpain), in addition to the possible underlying biochemical mechanisms. ASTX (1 mM) was capable of protecting lens crystallins from being oxidized, as measured by changes in tryptophan fluorescence, in the presence of a Fenton reaction solution containing 0.2 mM Fe<sup>2+</sup> and 2 mM H<sub>2</sub>O<sub>2</sub>. Sodium dodecyl sulfate-polyacrylamide gel electrophoresis analysis demonstrated that beta(high)-crystallin was the most vulnerable protein under these conditions of free radical exposure. The proteolysis of lens crystallins induced by calcium ion-activated calpain was also inhibited by ASTX (0.03-1 mM) as determined by daily measurement of the light-scattering intensity at 405 nm for five consecutive days. ASTX at 1 mM was as potent as a concentration of 0.1 mM calpain inhibitor E64 in protecting the oxidative damage/hydrolysis of porcine crystallins. At a concentration of 1 mM, ASTX provided better protection than the endogenous antioxidant glutathione in terms of suppressing calcium-induced turbidity of lens proteins. Thin-layer chromatography analysis indicated that ASTX interacted with calcium ions to form complexes, which we believe interfere with the hydrolysis of lens crystallins by calcium-activated calpain. This in vitro study shows that ASTX is capable of protecting porcine lens proteins from oxidative insults and degradation by calcium-induced calpain. Publication Types:

PMID: 16536628 [PubMed - indexed for MEDLINE]

Eye Health112

Exp Eye Res. 2006 Feb;82(2):275-81. Epub 2005 Aug 26.

**Suppressive effects of astaxanthin against rat endotoxin-induced uveitis by inhibiting the NF-kappaB signaling pathway.** Suzuki Y, Ohgami K, Shiratori K, Jin

XH, Ilieva I, Koyama Y, Yazawa K, Yoshida K, Kase S, Ohno S. Department of Ophthalmology and Visual Sciences, Hokkaido University Graduate School of Medicine, N15 W7, Sapporo 060-8638, Japan. We investigated the effects of astaxanthin (AST), a carotenoid, on endotoxin-induced uveitis (EIU), and over the course of the disease measured the expression of inflammatory cytokines and chemokines in the presence or absence of AST. EIU was induced in male Lewis rats by footpad injection of lipopolysaccharide (LPS). The animals were randomly divided to 12 groups with eight animals in each. Immediately after the inoculation, AST (1, 10, or 100 mg kg<sup>-1</sup>) was injected intravenously. Aqueous humour was collected at 6, 12 and 24 hr after LPS inoculation and the number of infiltrating cells in the anterior chamber was counted. In addition, we assayed the concentration of protein, nitric oxide (NO), tumour necrosis factor-alpha (TNF-alpha) and prostaglandin E2 (PGE2). Immunohistochemical staining with a monoclonal antibody against activated NF-kappaB was performed in order to evaluate the effects of AST on NF-kappaB activation. Rats injected with AST showed a significant decrease in the number of infiltrating cells in the anterior chamber and additionally there was a significantly lower concentration of protein, NO, TNF-alpha and PGE2 in the aqueous humour. Moreover, even early stages of EIU were suppressed by injection of AST. The number of activated NF-kappaB-positive cells was lower in iris-ciliary bodies treated with 10 or 100 mg kg<sup>-1</sup> AST at 3 hr after LPS injection. These results suggest that AST reduces ocular inflammation in eyes with EIU by downregulating proinflammatory factors and by inhibiting the NF-kappaB-dependent signaling pathway. Publication Types:

PMID: 16126197 [PubMed - indexed for MEDLINE]

Eye Health113

J Nutr. 2004 Dec;134(12):3225-32.

**Xanthophylls and alpha-tocopherol decrease UVB-induced lipid peroxidation and stress signaling in human lens epithelial cells. Chitchumroonchokchai C, Bomser JA, Glamm JE, Failla ML.**

Ohio State University Interdisciplinary PhD Program in Nutrition, Ohio State University, Columbus, OH 43210, USA. Epidemiological studies suggest that consumption of vegetables rich in the xanthophylls lutein (LUT) and zeaxanthin (ZEA) reduces the risk for developing age-related cataract, a leading cause of vision loss. Although LUT and ZEA are the only dietary carotenoids present in the lens, direct evidence for their photoprotective effect in this organ is not available. The present study examined the effects of xanthophylls and alpha-tocopherol (alpha-TC) on lipid peroxidation and the mitogen-activated stress signaling pathways in human lens epithelial (HLE) cells following ultraviolet B light (UVB) irradiation. When presented with LUT, ZEA, astaxanthin (AST), and alpha-TC as methyl-beta-cyclodextrin complexes, HLE cells accumulated the lipophiles in a concentration- and time-dependent manner with uptake of LUT exceeding that of ZEA and AST. Pretreatment of cultures with either 2 micromol/L xanthophyll or 10 micromol/L alpha-TC for 4 h before exposure to 300 J/m<sup>2</sup> UVB radiation decreased lipid peroxidation by 47-57% compared with UVB-treated control HLE cells. Pretreatment with the xanthophylls and alpha-TC also inhibited UVB-induced activation of c-JUN NH<sub>2</sub>-terminal kinase (JNK) and p38 by 50-60 and 25-32%, respectively. There was substantial inhibition of UVB-induced JNK and p38 activation for cells containing <0.20 and approximately 0.30 nmol xanthophylls/mg, respectively, whereas >2.3 nmol alpha-TC/mg protein was required to significantly decrease UVB-induced stress signaling. These data suggest that xanthophylls are more potent than alpha-TC for protecting human lens epithelial cells against UVB insult. Publication Types:

PMID: 15570017 [PubMed - indexed for MEDLINE]

Eye Health114

**Cataract formation in Atlantic salmon, *Salmo salar* L., smolt relative to dietary pro- and antioxidants and lipid level. Waagbø R, Hamre K, Bjerås E, Berge R, Wathne E, Lie O, Torstensen B.** National Institute of Nutrition and Seafood Research, Bergen, Norway.

rune.waagbo@nutr.fiskeridir.no The development of cataracts in Atlantic salmon, *Salmo salar* L., was studied in 16 groups of smolts fed diets differing in prooxidant (iron, copper, manganese) and antioxidant (vitamin E, vitamin C, astaxanthin) composition and lipid level for 23 weeks in sea water, using a 2(7-3) reduced factorial design. The seven dietary variables were systematically varied at low (requirement level and 150 g lipid kg<sup>-1</sup>) and high levels (below known toxic levels and 320 g lipid kg<sup>-1</sup>). A mean endpoint cataract incidence of approximately 36% was observed. High dietary levels of vitamin C and astaxanthin reduced cataract frequency, whereas high dietary lipid level, iron and manganese were associated with increased cataract frequencies. Considering the nutritional status of selected organs of the fish, only the status of ascorbic acid correlated negatively to cataract development ( $P < 0.05$ ). The lens glutathione (GSH) status was not correlated to cataract frequency, nor statistically explained by the dietary variables. However, the study shows that balancing the diet with respect to pro- and antioxidant nutrients may significantly protect Atlantic salmon against development of cataracts. An incidence of reversible osmotic cataract observed at week 14 was positively correlated to plasma glucose concentration. Publication Types:

PMID: 12962230 [PubMed - indexed for MEDLINE]

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**Effects of Astaxanthin on Accommodative Recovery**

TAKAHASHI NANAOKO (Kajitaganka) KAJITA MASAYOSHI (Kajitaganka)

Effects of astaxanthin on accommodative recovery derived from a rest after VDT (visual display terminal) working was studied. Ten healthy volunteers were entered into the study, and except one subject who developed allergic conjunctivitis during the study, 9 of whom were evaluated (9 dominant eyes) by values of objective diopter, HFC (High Frequency Component in Accommodative micro-fluctuation) and accommodative reaction. Consequently, increase of HFC after the rest was significantly restrained by astaxanthin uptake compared to that shortly after working. Therefore, Astaxanthin was suggested to have effects on accommodation during recovery process of accommodative fatigue to relieve fatigue rapidly.

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**Effects of astaxanthin on accommodation, critical flicker fusion, and pattern visual evoked potential in visual display terminal workers.**

NAGAKI Y; HAYASAKA S ; YAMADA T ; HAYASAKA Y; SANADA M; UONOMI T

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, 5mg/day, for 4 weeks, and Group C consisted of 13 subjects who received an oral placebo, 5mg/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 amplitude in Group A was 3.7. $\pm$ .1.5 diopters. Accommodation amplitudes (2.3. $\pm$ .1.4 and 2.2. $\pm$ .1.0 diopters) in Groups B and C before supplementation were significantly ( $p < 0.05$ ) lower than in Group A. Accommodation amplitude (2.8. $\pm$ .1.6 diopters) in Group B after astaxanthin treatment was significantly ( $p < 0.01$ ) larger than before supplementation, while accommodation amplitude (2.3. $\pm$ .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. $\pm$ .4.2Hz, 6.5 $\pm$ 1.8.MU.V, and 101.3. $\pm$ .6.5msec, respectively. The CFFs in Groups B and C before supplementation were significantly ( $p < 0.05$ ) lower than in Group A. The CFFs 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.

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**Effects of Astaxanthin on Accommodation and Asthenopia-Dose Finding Study in Healthy Volunteers-**

NITTA TAKUYA; OGAMI KAZUHIRO; SHIRATORI KENJI; SHINMEI YASUHIRO; CHIN SHINKI; YOSHIDA KAZUHIKO; TSUKAHARA HIROKI; ONO SHIGEAKI

A double-blind study was conducted in healthy volunteers to objectively evaluate the optimum dose and safety of astaxanthin (AX) on accommodation and asthenopia. The subjects were divided into 3 groups: 0mg (AX 0mg group), 6mg (AX 6mg group) and 12mg (AX 12mg group) of astaxanthin administered. Ten subjects, total thirty subjects were included in each group. Mean time consumed for close working (e.g., VDT working) was approximately 7 hours a day. The testing food was given to the subjects for 4 weeks. Then, the subjects were traced for 4 weeks and assessed by comparison of the observed values between pre- and post-dosing. As a result 1. Objective accommodation power of the AX 12mg group was significantly increased compared to that of pre-dosing. 2. Positive accommodation time was significantly shortened in the AX 6mg and the 12mg groups compared to those of pre-dosing, and negative accommodation time was significantly shortened in the AX 0mg and the 6mg groups compared to those of pre-dosing. 3. According to the assessment by VAS, many parameters in subjective symptoms were improved in the AX 6mg group. 4. No changes were noted in laboratory tests of controversial in clinical setting due to AX uptake. Also, there were no adverse events caused by the administration of the testing food. In conclusion, accommodation power and subjective symptoms relating asthenopia were improved by taking 6mg/day of astaxanthin, therefore more than 6mg/day was considered to be optimal dosage of astaxanthin.

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Bechettobyō ni kansuru Chōsa Kenkyū Heisei 14 Nendo Sokatsu, Buntan Kenkyū Hokokusho  
VOL.;NO.;PAGE.98-99(2003)

**Research on the anti-inflammatory effect of astaxanthin**

ONO SHIGEAKI; OGAMI KAZUHIRO; SHIRATORI KENJI; ILIEVA I; KOTAKE SATOSHI;  
NISHIDA TOMOMI; MIZUKI NOBUHISA

The effect of astaxanthin (AST) was examined in rat model of the endotoxin induced uveitis. As the result, the protein concentration in the hydatoid lowered obviously in the group which administered 10 (AST10) or 100mg/kg (AST100) of AST in comparison with control animals. The number of inflammatory cells was significantly decreased only in AST100 group. The effect of AST on protein concentration and cell numbers in the hydatoid in AST100 group was almost equivalent to those of 10mg/kg of prednisolone (PSL) administrated group. Any side effects by AST administration could not be observed. AST showed dose-dependent inhibitory effect in this model. Therefore, it was indicated that AST could be utilized as a new antiphlogistic for ophthalmia disease.

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Atarashii Ganka, 25(10):1461-1464 (In Japanese). 2008

### **Intraocular penetration of astaxanthin in rabbit eyes**

Fukuda et al.,

In a new study, natural astaxanthin extract derived from *Haematococcus microalgae* was detected in the iris/ciliary body of New Zealand Albino (NZW) Rabbit Eyes 24 hours after ingestion.

Astaxanthin has been reported to have many benefits in the eye. Several human clinical studies reported the alleviation of eye fatigue (by improving accommodation function) in visual display terminal (VDT) workers after oral supplementation. However, up to now there has been no intraocular kinetic information available. In collaboration between the Ophthalmology Department of Kanazawa Medical University, Japan, and Fuji Chemical Industry, Japan, researchers investigated the ocular and blood serum levels of astaxanthin in 24 NZW albino rabbits. After administering a 100 mg/kg single oral dose, astaxanthin was determined by careful extraction followed by HPLC analysis over a period of 168 hours. According to the astaxanthin detection system, the time taken to reach maximum presence (T<sub>max</sub>) in serum and iris/ciliary body was 9 hours (at C<sub>max</sub> 61.3 ng/mL) and 24 hours (at C<sub>max</sub> 79.3) respectively. In other human studies with oral intake of astaxanthin, the T<sub>max</sub> in serum ranged between 9 and 12 hours.

The intraocular penetration kinetics could have a similar pattern to humans but further study is necessary. This study adds to the growing body of science supporting astaxanthin's benefits for eye fatigue caused by VDT use.

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**Effects of Astaxanthin on Eyestrain Induced by Accommodative Dysfunction**

IWASAKI TSUNETO; TAHARA AKIHIKO

We investigated effects of astaxanthin on eyestrain induced by accommodative dysfunction. The 10 healthy subjects received 6mg/day of astaxanthin (Ax group) or 0mg/day (placebo; P group) for 14 days, and were then assigned a near visual task for 20min. Accommodative function and subjective symptoms relating to eyestrain were measured before and after the task, and after the 10-minute rest following the task. The data were then compared between Ax and P groups by the double-blind cross-over method. After the task, accommodation contraction and relaxation times were extended in both the Ax and P groups. Comparison between the two groups showed that after the task, accommodation relaxation time was significantly extended in P group, in contrast to Ax. Accommodative contraction and relaxation times were significantly prolonged after the 10-minute rest in P group as compared to Ax. 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.

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Journal of Traditional Medicines 2002: 19 (5), 170 – 173.

**Effects of Astaxanthin on accommodation, critical flicker fusion, and pattern visual evoked potential in visual display terminal workers.**

Nagaki Y., Hayasaka S., Yamada T., Hayasaka Y., Sanada M., Uonomi T.

Working for long periods at visual display terminals reportedly induces various visual problems such as eye strain, blurring and diplopia (a disorder of vision in which two images of a single object are seen because of unequal action of the eye muscles – also called double vision). In a double blind study performed in Japan, after four weeks of supplementation with 5 mg of Astaxanthin per day (extracted from *Haematococcus Pluvialis* algae meal) the authors reported a 46% reduction of eye strain subjects and higher accommodation amplitude in visual display terminal subjects.

Although the mechanism of action is unclear, Astaxanthin's potent antioxidant properties may relieve chronic stress of visual display terminal use that may induce hypofunction of the ciliary body, resulting in decreased accommodation.

Eye Health123

Invest Ophthalmol Vis Sci. 2003 Jun;44(6):2694-701

## **Effects of astaxanthin on lipopolysaccharide-induced inflammation in vitro and in vivo**

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**PURPOSE:** Astaxanthin (AST) is a carotenoid that is found in marine animals and vegetables. Several previous studies have demonstrated that AST exhibits a wide variety of biological activities including antioxidant, antitumor, and anti-*Helicobacter pylori* effects. In this study, attention was focused on the antioxidant effect of AST. The object of the present study was to investigate the efficacy of AST in endotoxin-induced uveitis (EIU) in rats. In addition, the effect of AST on endotoxin-induced nitric oxide (NO), prostaglandin E2 (PGE2), and tumor necrosis factor (TNF)-alpha production in a mouse macrophage cell line (RAW 264.7) was studied in vitro. **METHODS:** EIU was induced in male Lewis rats by a footpad injection of lipopolysaccharide (LPS). AST or prednisolone was administered intravenously at 30 minutes before, at the same time as, or at 30 minutes after LPS treatment. The number of infiltrating cells and protein concentration in the aqueous humor collected at 24 hours after LPS treatment was determined. RAW 264.7 cells were pretreated with various concentrations of AST for 24 hours and subsequently stimulated with 10 microg/mL of LPS for 24 hours. The levels of PGE2, TNF-alpha, and NO production were determined in vivo and in vitro. **RESULTS:** AST suppressed the development of EIU in a dose-dependent fashion. The anti-inflammatory effect of 100 mg/kg AST was as strong as that of 10 mg/kg prednisolone. AST also decreased production of NO, activity of inducible nitric oxide synthase (NOS), and production of PGE2 and TNF-alpha in RAW264.7 cells in vitro in a dose-dependent manner. **CONCLUSIONS:** This study suggests that AST has a dose-dependent ocular anti-inflammatory effect, by the suppression of NO, PGE2, and TNF-alpha production, through directly blocking NOS enzyme activity.

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**The Effect of Astaxanthin on Retinal Capillary Blood Flow in Normal Volunteers**

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HORITA YOSHIHARU; SUGIURA YURI; TSUKAHARA HIROKI

Objective: 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: 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 by the Heidelberg Retina Flowmeter. Changes in blood pressure, blood cell counts, fasting plasma glucose level, fasting plasma astaxanthin level, retinal capillary blood flow, intraocular pressure, inquiry about eye strain were examined 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.

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**Sports Performance Benefits from Taking Natural Astaxanthin Characterized by Visual Acuity and Muscle Fatigue Improvement in Humans.**

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AZUMANE AKITO; KANEKO KESATOKI; YAMAGUCHI MASAHIRO

The effects of astaxanthin on visual acuity and muscle fatigue were studied. Astaxanthin (3,3'-Dihydroxy-.BETA.,.BETA.-carotene-4,4'-dione) is a red pigment found in salmon and krill and has strong antioxidant properties. In the two supplementation studies, astaxanthin extracted from algae (*Haematococcus pluvialis*) was used. Four visual acuity parameters were examined in experiment A in 18 healthy adult male volunteers that were equally divided into two groups (treatment and control). The measured parameters were deep vision, critical flicker fusion, static and kinetic visual acuity before and after supplementation. A second investigation (experiment B) involved 16 adult male volunteers to establish the effect of astaxanthin supplementation on the build up of lactic acid before and after running 1200 metres. In both experiments, the treated groups ingested an astaxanthin capsule per day for 4 weeks (6mg astaxanthin per day) and the control groups received a placebo capsule. Results: In experiment A, the deep vision and the critical flicker fusion of the treated groups were significantly improved compared to the control group. No effects of treated group were observed on static and kinetic visual acuity. In experiment B, serum lactic acid concentration at 2 minutes after activity (1,200m running) of the treatment group was significantly lower than that of the control one. No other effects related to supplementation of astaxanthin on serum biological and hematological examinations were observed. Based on these preliminary findings, it suggested that supplementation of astaxanthin is effective for the improvement of visual acuity and muscle fatigue that may lead to sports performance benefits.

Eye Health126

Regul Toxicol Pharmacol. 2010 Oct;58(1):121-30. Epub 2010 May 8.

**Suppressive effect of astaxanthin on retinal injury induced by elevated intraocular pressure.** Cort A, Ozturk N, Akpinar D, Unal M, Yucel G, Ciftcioglu A,

Yargicoglu P, Aslan M.

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**Abstract**

The aim of this study was to clarify the possible protective effect of astaxanthin (ASX) on the retina in rats with elevated intraocular pressure (EIOP). Rats were randomly divided into two groups which received olive oil or 5mg/kg/day ASX for a period of 8 weeks. Elevated intraocular pressure was induced by unilaterally cauterizing three episcleral vessels and the unoperated eye served as control. At the end of the experimental period, neuroprotective effect of ASX was determined via electrophysiological measurements of visual evoked potentials (VEP) and rats were subsequently sacrificed to obtain enucleated globes which were divided into four groups including control, ASX treated, EIOP, EIOP+ASX treated. Retinoprotective properties of ASX were determined by evaluating retinal apoptosis, protein carbonyl levels and nitric oxide synthase-2 (NOS-2) expression. Latencies of all VEP components were significantly prolonged in EIOP and returned to control levels following ASX administration. When compared to controls, EIOP significantly increased retinal protein oxidation which returned to baseline levels in ASX treated EIOP group. NOS-2 expression determined by Western blot analysis and immunohistochemical staining was significantly greater in rats with EIOP compared to ASX and control groups. Retinal TUNEL staining showed apoptosis in all EIOP groups; however ASX treatment significantly decreased the percent of apoptotic cells when compared to non treated ocular hypertensive controls. The presented data confirm the role of oxidative injury in EIOP and highlight the protective effect of ASX in ocular hypertension.

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J Agric Food Chem. 2006 Mar 22;54(6):2418-23.

## **Astaxanthin protects against oxidative stress and calcium-induced porcine lens protein degradation.**

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Astaxanthin (ASTX), a carotenoid with potent antioxidant properties, exists naturally in various plants, algae, and seafoods. In this study, we investigated the in vitro ability of ASTX to protect porcine lens crystallins from oxidative damage by iron-mediated hydroxyl radicals or by calcium ion-activated protease (calpain), in addition to the possible underlying biochemical mechanisms. ASTX (1 mM) was capable of protecting lens crystallins from being oxidized, as measured by changes in tryptophan fluorescence, in the presence of a Fenton reaction solution containing 0.2 mM Fe<sup>2+</sup> and 2 mM H<sub>2</sub>O<sub>2</sub>. Sodium dodecyl sulfate-polyacrylamide gel electrophoresis analysis demonstrated that beta(high)-crystallin was the most vulnerable protein under these conditions of free radical exposure. The proteolysis of lens crystallins induced by calcium ion-activated calpain was also inhibited by ASTX (0.03-1 mM) as determined by daily measurement of the light-scattering intensity at 405 nm for five consecutive days. ASTX at 1 mM was as potent as a concentration of 0.1 mM calpain inhibitor E64 in protecting the oxidative damage/hydrolysis of porcine crystallins. At a concentration of 1 mM, ASTX provided better protection than the endogenous antioxidant glutathione in terms of suppressing calcium-induced turbidity of lens proteins. Thin-layer chromatography analysis indicated that ASTX interacted with calcium ions to form complexes, which we believe interfere with the hydrolysis of lens crystallins by calcium-activated calpain. This in vitro study shows that ASTX is capable of protecting porcine lens proteins from oxidative insults and degradation by calcium-induced calpain.

PMID: 16536628 [PubMed - indexed for MEDLIN

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# **Astaxanthin, a dietary carotenoid, protects retinal cells against oxidative stress in-vitro and in mice in-vivo.**

Nakajima Y, Inokuchi Y, Shimazawa M, Otsubo K, Ishibashi T, Hara H.

## **Source**

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## **Abstract**

We have investigated whether astaxanthin exerted neuroprotective effects in retinal ganglion cells in-vitro and in-vivo. In-vitro, retinal damage was induced by 24-h hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>) exposure or serum deprivation, and cell viability was measured using a WST assay. In cultured retinal ganglion cells (RGC-5, a rat ganglion cell-line transformed using E1A virus), astaxanthin inhibited the neurotoxicity induced by H<sub>2</sub>O<sub>2</sub> or serum deprivation, and reduced the intracellular oxidation induced by various reactive oxygen species (ROS). Furthermore, astaxanthin decreased the radical generation induced by serum deprivation in RGC-5. In mice in-vivo, astaxanthin (100 mg kg<sup>-1</sup>, p.o., four times) reduced the retinal damage (a decrease in retinal ganglion cells and in thickness of inner plexiform layer) induced by intravitreal N-methyl-D-aspartate (NMDA) injection. Furthermore, astaxanthin reduced the expressions of 4-hydroxy-2-nonenal (4-HNE)-modified protein (indicator of lipid peroxidation) and 8-hydroxy-deoxyguanosine (8-OHdG; indicator of oxidative DNA damage). These findings indicated that astaxanthin had neuroprotective effects against retinal damage in-vitro and in-vivo, and that its protective effects may have been partly mediated via its antioxidant effects.

PMID: 18812030 [PubMed - indexed for MEDLINE]

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