The Medical Research of Astaxanthin

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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 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 the pristine Kona Coast of Hawaii.

Antioxidant

Carotenoid Science, Vol.11, 2007, 16-20

Quenching Activities of Common Hydrophilic and Lipophilic Antioxidants against Singlet Oxygen Using Chemiluminescence Detection System

Yasuhiro Nishida*, Eiji Yamashita and Wataru Miki
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The singlet oxygen quenching activities among common hydrophilic and lipophilic antioxidants such as polyphenols, tocopherols, carotenoids, ascorbic acid, coenzyme Q10 and α-lipoic acid were recorded under the same test condition: the chemiluminescence detection system for direct 1O2 counting using the thermodissociable endoperoxides of 1,4-dimethylnaphthalene as 1O2 generator in DMF : CDCl3 (9 : 1). Carotenoids exhibited larger total quenching rate constants than other antioxidants, with astaxanthin showing the strongest activity. α-Tocopherol and α-lipoic acid showed considerable activities, whereas the activities of ascorbic acid, CoQ10 and polyphenols were only slight; these included capsaicin, probucol, edaravon, BHT and Trolox. This system has the potential of being a powerful tool to evaluate the quenching activity against singlet oxygen for various hydrophilic and lipophilic compounds.

Adapted from Nishida, Yamashita, Miki, Carotenoid Science, Vol. 11, 2007, 16-20 (in Japanese)

Astaxanthin has exceptional antioxidant activity to combat singlet oxygen when compared to other antioxidants. In particular, Astaxanthin can be used to defend against singlet oxygen damage for eye and skin health, which are especially susceptible to UV damage and aging effects.

Singlet oxygen is an active oxygen species generated in human skin by exposure to ultraviolet radiation (UV) that causes skin damage and eye damage. In this study, Astaxanthin extracted from *Haematococcus* microalgae powerfully quenched singlet oxygen. Results show that the quenching effect of Astaxanthin is 800 times greater than coenzyme Q10. Astaxanthin was also about 75 times greater than alpha lipoic acid, about 550 times greater than green tea catechins and about 6000 times greater than Vitamin C.

Antioxidant

Carotenoids as Singlet Oxygen Quenchers in Marine Organisms

Shimidzu, Gogo, Miki, 1995. Fisheries Science 62(1), 134-137

Results indicated that Astaxanthin was significantly stronger than all other antioxidants tested as singlet oxygen quenchers. Among the results Astaxanthin was shown to be 550X stronger than Vitamin E; 11X stronger than Beta-Carotene; 2.75X stronger than Lutein.

Antioxidant

OXYGEN FREE RADICAL SCAVENGING ABILITIES OF VITAMINS C, E, β-CAROTENE, PYCNOGENOL, GRAPE SEED PROANTHOCYANIDIN EXTRACT AND ASTAXANTHINS *IN VITRO*

Debasis Bagchi, Ph.D. Pharmacy Sciences, Creighton University School of Health Sciences, June 2001

Summary: Natural Astaxanthin (as BioAstin® from Cyanotech) showed significantly higher free radical scavenging activity than all other antioxidants tested. Results on a pure active basis were as follows:

Natural Astaxanthin	Alternate Antioxidant	Multiple of Greater Free Radical Scavenging Activity
BioAstin	Vitamin C	65X stronger
BioAstin	Vitamin E	14X stronger
BioAstin	Beta Carotene	54X stronger
BioAstin	Pycnogenol®	18X stronger
BioAstin	Synthetic Astaxanthin	21X stronger

Antioxidant

Comparison of Astaxanthin's Singlet Oxygen Quenching Activity with Common Fat and Water Soluble Antioxidants

United States Patent Application ***20060217445***
Kind Code **A1**
Chew; Boon P. ; et al. **September 28, 2006**

Natural astaxanthin extract reduces DNA oxidation

Abstract

Provided herein are methods for reducing oxidative DNA damage in a subject, by administering to the subject astaxanthin, for instance a natural, astaxanthin-enriched extract from Haematococcus pluvialis. It is shown that doses as low as 2 mg/day, given orally to a human subject for a period of four weeks, is sufficient to reduced measurable endogenous oxidative DNA damage by about 40%.

Antioxidant

Phytother Res. 2009 Jun 22. [Epub ahead of print]

Cytoprotective role of astaxanthin against glycated protein/iron chelate-induced toxicity in human umbilical vein endothelial cells.

Nishigaki I, **Rajendran P**, **Venugopal R**, **Ekambaram G**, **Sakthisekaran D**, **Nishigaki Y**.

NPO International Laboratory of Biochemistry, 1-166 Uchide, Nakagawa-ku Nagoya 454-0926, Japan.

Astaxanthin (ASX), a red carotenoid pigment with no pro-vitamin A activity, is a biological antioxidant that occurs naturally in a wide variety of plants, algae and seafoods. This study investigated whether ASX could inhibit glycated protein/iron chelate-induced toxicity in human umbilical-vein endothelial cells (HUVEC) by interfering with ROS generation in these cells. Glycated fetal bovine serum (GFBS) was prepared by incubating fetal bovine serum (FBS) with high-concentration glucose. Stimulation of cultured HUVECs with 50 mm 1 mL of GFBS significantly enhanced lipid peroxidation and decreased antioxidant enzyme activities and levels of phase II enzymes. However, preincubation of the cultures with ASX resulted in a marked decrease in the level of lipid peroxide (LPO) and an increase in the levels of antioxidant enzymes in an ASX concentration-dependent manner. These results demonstrate that ASX could inhibit LPO formation and enhance the antioxidant enzyme status in GFBS/iron chelate-exposed endothelial cells by suppressing ROS generation, thereby limiting the effects of the AGE-RAGE interaction. The results indicate that ASX could have a beneficial role against glycated protein/iron chelate-induced toxicity by preventing lipid and protein oxidation and increasing the activity of antioxidant enzymes.

PMID: 19548280 [PubMed - as supplied by publisher]

Antioxidant

Biochim Biophys Acta. 2001 Jun 6;1512(2):251-8.

Efficient radical trapping at the surface and inside the phospholipid membrane is responsible for highly potent antiperoxidative activity of the carotenoid astaxanthin.

Goto S, **Kogure K**, **Abe K**, **Kimata Y**, **Kitahama K**, **Yamashita E**, **Terada H**.

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The effects of the carotenoids beta-carotene and astaxanthin on the peroxidation of liposomes induced by ADP and Fe(2+) were examined. Both compounds inhibited production of lipid peroxides, astaxanthin being about 2-fold more effective than beta-carotene. The difference in the modes of destruction of the conjugated polyene chain between beta-carotene and astaxanthin suggested that the conjugated polyene moiety and terminal ring moieties of the more potent astaxanthin trapped radicals in the membrane and both at the membrane surface and in the membrane, respectively, whereas only the conjugated polyene chain of beta-carotene was responsible for radical trapping near the membrane surface and in the interior of the membrane. The efficient antioxidant activity of astaxanthin is suggested to be due to the unique structure of the terminal ring moiety.

Publication Types:

PMID: 11406102 [PubMed - indexed for MEDLINE]

Antioxidant

Chem Biol Interact. 2009 Aug 14;180(3):398-406. Epub 2009 Apr 2.

Intervention of astaxanthin against cyclophosphamide-induced oxidative stress and DNA damage: a study in mice.

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Astaxanthin, a natural and nutritional red carotenoid pigment, is used as a dietary supplement. The intention of the present study was to investigate the beneficial effects of dietary pigment astaxanthin, against cyclophosphamide-induced oxidative stress and DNA damage. The end points of evaluation of the study included: (a) malondialdehyde, glutathione and superoxide dismutase concentration in liver to detect oxidative stress; (b) normal and modified alkaline comet assays (the latter includes lesion-specific enzymes formamidopyrimidine-DNA glycosylase and endonuclease-III) to detect normal and oxidative stress-induced DNA damage by cyclophosphamide in the mouse bone marrow and the peripheral blood lymphocytes. In addition, micronucleus assay and chromosomal aberration test capable of detecting the DNA damage were also carried out in peripheral blood and bone marrow of mice. Cyclophosphamide (100 mg/kg intra-peritoneal) treatment led to significant increase in liver malondialdehyde and decreased the antioxidant enzymes glutathione and superoxide dismutase. Further, cyclophosphamide also significantly increased the DNA damage as observed from normal and modified comet assays as well as micronucleus and chromosomal aberration assay. Pre-treatment with astaxanthin (12.5, 25 and 50 mg/kg/day for 5 days per oral) resulted in the restoration of oxidative stress markers such as malondialdehyde, glutathione and superoxide dismutase in liver. The amelioration of oxidative stress with astaxanthin pre-treatment correlated well with the decreased DNA damage as evident from normal and modified alkaline comet assays of bone marrow cells and peripheral blood lymphocytes. Further astaxanthin pre-treatment also reduced the frequency of chromosomal breakage and micronucleus formation in the mouse bone marrow cells and peripheral blood reticulocytes. It is thus concluded that pre-treatment with astaxanthin attenuates cyclophosphamide-induced oxidative stress and subsequent DNA damage in mice and it can be used as a chemoprotective agent against the toxicity of anticancer drug cyclophosphamide.

Research Support, Non-U.S. Gov't
PMID: 19539803 [PubMed - in process]

Antioxidant

J Agric Food Chem. 2000 Apr;48(4):1150-4.

Antioxidant activities of astaxanthin and related carotenoids.

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Phytochem Technologies, Chelmsford, MA 01824, USA.

The antioxidant activities of astaxanthin and related carotenoids have been measured by employing a newly developed fluorometric assay. This assay is based on 4,4-difluoro-3,5-bis(4-phenyl-1, 3-butadienyl)-4-bora-3a,4a-diaza-s-indacene (BODIPY 665/676) as an indicator; 2,2'-azobis-2,4-dimethylvaleronitrile (AMVN) as a peroxyl radical generator; and 6-hydroxy-2,5,7, 8-tetramethylchroman-2-carboxylic acid (Trolox) as a calibrator in an organic and liposomal media. By employing this assay, three categories of carotenoids were examined: namely, the hydrocarbon carotenoids lycopene, alpha-carotene, and beta-carotene; the hydroxy carotenoid lutein; and the alpha-hydroxy-ketocarotenoid astaxanthin. The relative peroxyl radical scavenging activities of Trolox, astaxanthin, alpha-tocopherol, lycopene, beta-carotene, lutein, and alpha-carotene in octane/butyronitrile (9:1, v/v) were determined to be 1.0, 1.0, 1.3, 0.5, 0.4, 0.3, and 0.2, respectively. In dioleoylphosphatidyl choline (DOPC) liposomal suspension in Tri-HCl buffer (pH 7.4 at 40 degrees C), the relative reactivities of astaxanthin, beta-carotene, alpha-tocopherol, and lutein were found to be 1.00, 0.9, 0.6, and 0.6, respectively. When BODIPY 665/676 was replaced by 4,4-difluoro-5-(4-phenyl-1,3-butadienyl)-4-bora-3a, 4a-diaza-s-indacene-3-undecanoic acid (BODIPY 581/591 C(11)) as an indicator, astaxanthin showed the highest antioxidant activity toward peroxyl radicals. The relative reactivities of Trolox, astaxanthin, alpha-tocopherol, alpha-carotene, lutein, beta-carotene, and lycopene were determined to be 1.0, 1.3, 0.9, 0.5, 0.4, 0.2, and 0.4, respectively.

PMID: 10775364 [PubMed - indexed for MEDLINE]

J Nutr Biochem. 2009 May 6. [Epub ahead of print]

Astaxanthin protects mitochondrial redox state and functional integrity against oxidative stress.

Wolf AM, **Asoh S**, **Hiranuma H**, **Ohsawa I**, **Iio K**, **Satou A**, **Ishikura M**, **Ohta S**.

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Mitochondria combine the production of energy with an efficient chain of reduction-oxidation (redox) reactions but also with the unavoidable production of reactive oxygen species. Oxidative stress leading to mitochondrial dysfunction is a critical factor in many diseases, such as cancer and neurodegenerative and lifestyle-related diseases. Effective antioxidants thus offer great therapeutic and preventive promise. Investigating the efficacy of antioxidants, we found that a carotenoid, astaxanthin (AX), decreased physiologically occurring oxidative stress and protected cultured cells against strong oxidative stress induced with a respiratory inhibitor. Moreover, AX improved maintenance of a high mitochondrial membrane potential and stimulated respiration. Investigating how AX stimulates and interacts with mitochondria, a redox-sensitive fluorescent protein (roGFP1) was stably expressed in the cytosol and mitochondrial matrix to measure the redox state in the respective compartments. AX at nanomolar concentrations was effective in maintaining mitochondria in a reduced state. Additionally, AX improved the ability of mitochondria to remain in a reduced state under oxidative challenge. Taken together, these results suggest that AX is effective in improving mitochondrial function through retaining mitochondria in the reduced state.

PMID: 19423317 [PubMed - as supplied by publisher]

Antioxidant

Zhongguo Gu Shang. 2008 Mar;21(3):187-9.

[Effects of Astaxanthin on the damage of osteoblast induced by H2O2]

[Article in Chinese]

Pei LP, **Dong FH**, **Hui BD**.

Institute of Orthopaedics and Traumatology, China Academy of Chinese Medical Science, Beijing 100700, China.

OBJECTIVE: To investigate the effect of Astaxanthin on enhancing the function of anti-oxidative damage in osteoblast. METHODS: MC3T3-E1 osteoblasts were randomly divided into five groups, including control group, model group, Astaxanthin group [low-dose (1 x 10(-7) mol/L), middle-dose (1 x 10(-6) mol/L), high-dose (1 x 10(-5) mol/L)], in which the activity of cells, activity of superoxide dismutase (SOD), the content of reactive oxygen species (ROS), lipid oxygen (LPO) and membrane fluidity were tested and compared. RESULTS: Compared with Astaxanthin groups, the activity of cells, SOD activity and membrane fluidity in the model group were significantly decreased ($P < 0.01$). However, the contents of ROS and LPO were significantly raised ($P < 0.01$). CONCLUSION: H2O2 can cause oxidative damage of MC3T3-E1 osteoblasts, but Astaxanthin can prevent or decrease its influence.

PMID: 19105434 [PubMed - indexed for MEDLINE]

Antioxidant

Phys Chem A. 2008 Sep 25;112(38):9037-42. Epub 2008 Aug 21.

Donator acceptor map for carotenoids, melatonin and vitamins.

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Bright yellow and red colors in animals and plants are assumed to be caused by carotenoids (CAR). In animals, these pigments are deposited in scales, skin and feathers. Together with other naturally occurring and colorless substances such as melatonin and vitamins, they are considered antioxidants due to their free-radical-scavenging properties. However, it would be better to refer to them as "antiradicals", an action that can take place either donating or accepting electrons. In this work we present quantum chemical calculations for several CAR and some colorless antioxidants, such as melatonin and vitamins A, C and E. The antiradical capacity of these substances is determined using vertical ionization energy (I), electron affinity (A), the electrodonating power (omega(-)) and the electroaccepting power (omega(+)). Using fluor and sodium as references, electron acceptance (R(a)) and electron donation (R(d)) indexes are defined. A plot of R(d) vs R(a) provides a donator acceptor map (DAM) useful to classify any substance regarding its electron donating-accepting capability. Using this DAM, a qualitative comparison among all the studied compounds is presented. According to R(d) values, vitamin E is the most effective antiradical in terms of its electron donor capacity, while the most effective antiradical in terms of its electron acceptor capacity, R(a), is astaxanthin, the reddest CAR. These results may be helpful for understanding the role played by naturally occurring pigments, acting as radical scavengers either donating or accepting electrons.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 18714976 [PubMed - indexed for MEDLINE]

Antioxidant

Food Chem Toxicol. 2008 Jan;46(1):212-9. Epub 2007 Aug 14.

Effect of astaxanthin on kidney function impairment and oxidative stress induced by mercuric chloride in rats.

Augusti PR, **Conterato GM**, **Somacal S**, **Sobieski R**, **Spohr PR**, **Torres JV**, **Charão MF**, **Moro AM**, **Rocha MP**, **Garcia SC**, **Emanuelli T**.

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Reactive oxygen species are implicated as mediators of tissue damage in the acute renal failure induced by inorganic mercury. Astaxanthin (ASX), a carotenoid with potent antioxidant properties, exists naturally in various plants, algae, and seafoods. This paper evaluated the ability of ASX to prevent HgCl(2) nephrotoxicity. Rats were injected with HgCl(2) (0 or 5 mg/kg b.w., sc) 6h after ASX had been administered (0, 10, 25, or 50mg/kg, by gavage) and were killed 12h after HgCl(2) exposure. Although ASX prevented the increase of lipid and protein oxidation and attenuated histopathological changes caused by HgCl(2) in kidney, it did not prevent creatinine increase in plasma and delta-aminolevulinic acid dehydratase inhibition induced by HgCl(2). Glutathione peroxidase and catalase activities were enhanced, while superoxide dismutase activity was depressed in HgCl(2)-treated rats when compared to control and these effects were prevented by ASX. Our results indicate that ASX could have a beneficial role against HgCl(2) toxicity by preventing lipid and protein oxidation, changes in the activity of antioxidant enzymes and histopathological changes.

Publication Types:

PMID: 17881112 [PubMed - indexed for MEDLINE]

Antioxidant

Biochem Biophys Res Commun. 2007 May 25;357(1):187-93. Epub 2007 Mar 28.

Cis astaxanthin and especially 9-cis astaxanthin exhibits a higher antioxidant activity in vitro compared to the all-trans isomer.

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In recent years, a number of studies have implicated the potent antioxidant property of astaxanthin in various experimental systems; however, these studies employed only the all-trans isomer. On the other hand, it has been reported that all-trans natural astaxanthin is readily isomerized to cis-trans, especially 9-cis and 13-cis isomers, under certain conditions by chemical analysis; however, the biological activities of the cis isomers of astaxanthin are little known. In the present study, we investigated the antioxidant activity of 9-cis and 13-cis astaxanthin compared to the all-trans isomer in vitro. In a stable radical DPPH scavenging activity test and in rat microsome and rabbit erythrocyte ghost membrane lipid peroxidation systems induced by AAPH and t-BuOOH, respectively, the results apparently showed that cis-astaxanthin, especially 9-cis astaxanthin, exhibited a higher antioxidant effect than the all-trans isomer. In addition, during polyunsaturated fatty acid (PUFA) oxidation, both DHA and linoleic acid hydroperoxides formation were markedly inhibited by astaxanthin isomers addition in the order 9-cis >13-cis >all-trans. Furthermore, 9-cis also exhibited the most effective inhibition of the generation of ROS induced by 6-hydroxydopamine (6-OHDA) in human neuroblastoma SH-SY5Y cells among the astaxanthin isomers, as well as on the degradation of collagen type II induced by DHA and linoleic acid hydroperoxides. The above-mentioned results suggest, for the first time, that cis isomer astaxanthin, especially 9-cis astaxanthin, has a much higher antioxidant potency than that of the all-trans isomer.

PMID: 17416351 [PubMed - indexed for MEDLINE]

Antioxidant

Biochim Biophys Acta. 2007 Jan;1768(1):167-74. Epub 2006 Sep 22.

Differential effects of carotenoids on lipid peroxidation due to membrane interactions: X-ray diffraction analysis.

McNulty HP, **Byun J**, **Lockwood SF**, **Jacob RF**, **Mason RP**.

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The biological benefits of certain carotenoids may be due to their potent antioxidant properties attributed to specific physico-chemical interactions with membranes. To test this hypothesis, we measured the effects of various carotenoids on rates of lipid peroxidation and correlated these findings with their membrane interactions, as determined by small angle X-ray diffraction approaches. The effects of the homochiral carotenoids (astaxanthin, zeaxanthin, lutein, beta-carotene, lycopene) on lipid hydroperoxide (LOOH) generation were evaluated in membranes enriched with polyunsaturated fatty acids. Apolar carotenoids, such as lycopene and beta-carotene, disordered the membrane bilayer and showed a potent pro-oxidant effect (>85% increase in LOOH levels) while astaxanthin preserved membrane structure and exhibited significant antioxidant activity (40% decrease in LOOH levels). These findings indicate distinct effects of carotenoids on lipid peroxidation due to membrane structure changes. These contrasting effects of carotenoids on lipid peroxidation may explain differences in their biological activity.

PMID: 17070769 [PubMed - indexed for MEDLINE]

Antioxidant

Luminescence. 2005 Nov-Dec;20(6):419-27.

Comparative study of antioxidants as quenchers or scavengers of reactive oxygen species based on quenching of MCLA-dependent chemiluminescence.

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The quenching or scavenging effect of non-enzymatic antioxidants against reactive oxygen species (ROS) was studied by comparing the degree of suppression of chemiluminescence (CL) caused by the oxidation of MCLA (methoxylated Cypridina luciferin analogue) by ROS. MCLA-dependent CL caused by O2- was effectively quenched by ascorbic acid, beta-carotene, lycopene and astaxanthin, while it was enhanced by alpha-tocopherol. The CL by 1O2 was quenched effectively by beta-carotene, lycopene and astaxanthin, moderately by ascorbic acid, and slightly by alpha-tocopherol. beta-Carotene and alpha-tocopherol remarkably suppressed the CL when ROS was HO*. The present study revealed that MCLA-dependent CL assay provides a simple and rapid method for the evaluation of antioxidants as a quencher or scavenger against any kind of ROS. (c) 2005 John Wiley & Sons, Ltd.

Publication Types:

PMID: 15966055 [PubMed - indexed for MEDLINE]

Antioxidant

Bioorg Med Chem Lett. 2004 Aug 2;14(15):3985-91.

Synthesis, characterization, and direct aqueous superoxide anion scavenging of a highly water-dispersible astaxanthin-amino acid conjugate.

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The aqueous solubility and/or dispersibility of synthetic carotenoid analogs can be improved by varying the chemical structure(s) of the esterified moieties. In the current study, a highly water-dispersible astaxanthin (3,3'-dihydroxy-beta,beta-carotene-4,4'-dione) derivative was synthesized by esterification to the amino acid L-lysine, and subsequently converted to the tetrahydrochloride salt. Deep violet, evenly colored aqueous suspensions were obtained with addition of the novel derivative to USP purified water up to a maximum of 181.6 mg/mL. These aqueous suspensions were obtained without the addition of heat, detergents, co-solvents, or other additives. At higher concentrations (above 181.6 mg/mL), the dispersion became turbid and viscous. There was no saturation point up to 181.6 mg/mL. The direct superoxide scavenging ability of the tetrahydrochloride dilysine astaxanthin salt was also evaluated by electron paramagnetic resonance (EPR) spectroscopy in a well-characterized in vitro isolated human neutrophil assay. The novel derivative was an extremely potent (micromolar concentration) aqueous-phase scavenger, with near-complete suppression of the superoxide anion signal (as detected by spin-trap adducts of DEPMPO) achieved at 100 microM. To the authors' knowledge, this novel carotenoid derivative exhibits the greatest aqueous dispersibility yet described for a natural and/or synthetic C40 carotenoid, and as such, will find utility in those applications for which aqueous-phase singlet oxygen quenching and direct radical scavenging are required.

PMID: 15225712 [PubMed - indexed for MEDLINE]

Antioxidant

Chem Phys Lipids. 2001 Nov;113(1-2):11-22.

Molecular characteristics of astaxanthin and beta-carotene in the phospholipid monolayer and their distributions in the phospholipid bilayer.

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The molecular characteristics of the monolayers of astaxanthin with polar group on the beta-ionone ring in the molecule and beta-carotene without polar group and their interactions in mixed carotenoid-phospholipid monolayers and the effects of carotenoids on the phase behavior of the phospholipid bilayers were examined by the monolayer technique and differential scanning calorimetry (DSC). We found from the monolayer study that beta-carotene had an amphiphilic nature. The molecular assembly of astaxanthin in the monolayer at the hydrophobic/hydrophilic interface was more stable than that of beta-carotene. Dimyristoylphosphatidylcholine (DMPC) in the monolayer was miscible with astaxanthin in the range of 0-0.4 mol fractions of astaxanthin, but not fully miscible with beta-carotene even at low concentrations below 0.1 mol fraction of beta-carotene. Surface potential and compression/expansion cycles of beta-carotene monolayer indicated the formation of molecular aggregates by itself. DSC study showed that when small amount of astaxanthin was added, the transition temperature of dipalmitoylphosphatidylcholine (DPPC) was markedly shifted to lower temperatures and that the transition peak was asymmetrically broadened, indicative of a significant depression in cooperativity of the gel to liquid-crystalline transition. The asymmetric DSC endothermic bands of DPPC incorporating small amounts of astaxanthin were well fit by deconvolution into two to three domains containing different concentrations of astaxanthin. On the contrary, the incorporation of beta-carotene resulted in a small depression of the main transition temperature with a slight broadening of the transition peak, suggesting a small miscibility of beta-carotene with the phospholipid bilayer or a formation of aggregates of beta-carotene in the membranes. These results suggest that there would be a high localized concentration in the phase separated membrane for astaxanthin or beta-carotene to function effectively as scavenger.

PMID: 11687223 [PubMed - indexed for MEDLINE]

Antioxidant

Biochem Biophys Res Commun. 2001 Oct 19;288(1):225-32.

Astaxanthin and peridinin inhibit oxidative damage in Fe(2+)-loaded liposomes: scavenging oxyradicals or changing membrane permeability?

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Astaxanthin and peridinin, two typical carotenoids of marine microalgae, and lycopene were incorporated in phosphatidylcholine multilamellar liposomes and tested as inhibitors of lipid oxidation. Contrarily to peridinin results, astaxanthin strongly reduced lipid damage when the lipoperoxidation promoters-H(2)O(2), tert-butyl hydroperoxide (t-ButOOH) or ascorbate-and Fe(2+):EDTA were added simultaneously to the liposomes. In order to check if the antioxidant activity of carotenoids was also related to their effect on membrane permeability, the peroxidation processes were initiated by adding the promoters to Fe(2+)-loaded liposomes (encapsulated in the inner aqueous solution). Despite that the rigidifying effect of carotenoids in membranes was not directly measured here, peridinin probably has decreased membrane permeability to initiators (t-ButOOH > ascorbate > H(2)O(2)) since its incorporation limited oxidative damage on iron-liposomes. On the other hand, the antioxidant activity of astaxanthin in iron-containing vesicles might be derived from its known rigidifying effect and the inherent scavenging ability.

Publication Types:

PMID: 11594777 [PubMed - indexed for MEDLINE]

Antioxidant

Arch Biochem Biophys. 2001 Jan 1;385(1):13-9.

The interaction of dietary carotenoids with radical species.

Mortensen A, **Skibsted LH**, **Truscott TG**.

Department of Dairy and Food Science, Royal Veterinary and Agricultural University, Frederiksberg, Denmark.

Dietary carotenoids react with a wide range of radicals such as CCl3O2*, RSO2*, NO2*, and various arylperoxyl radicals via electron transfer producing the radical cation of the carotenoid. Less strongly oxidizing radicals, such as alkylperoxyl radicals, can lead to hydrogen atom transfer generating the neutral carotene radical. Other processes can also arise such as adduct formation with sulphur-centered radicals. The oxidation potentials have been established, showing that, in Triton X-100 micelles, lycopene is the easiest carotenoid to oxidize to its radical cation and astaxanthin is the most difficult. The interaction of carotenoids and carotenoid radicals with other antioxidants is of importance with respect to anti- and possibly pro-oxidative reactions of carotenoids. In polar environments the vitamin E (alpha-tocopherol) radical cation is deprotonated (TOH*+ --> TO* + H+) and TO* does not react with carotenoids, whereas in nonpolar environments such as hexane, TOH*+ is converted to TOH by hydrocarbon carotenoids. However, the nature of the reaction between the tocopherol and various carotenoids shows a marked variation depending on the specific tocopherol homologue. The radical cations of the carotenoids all react with vitamin C so as to "repair" the carotenoid.

Publication Types:

- Research Support, Non-U.S. Gov't
- Review

PMID: 11361009 [PubMed - indexed for MEDLINE]

Antioxidant

J Nutr. 2000 Jul;130(7):1800-8.

Depletion of alpha-tocopherol and astaxanthin in Atlantic salmon (Salmo salar) affects autoxidative defense and fatty acid metabolism.

Bell JG, **McEvoy J**, **Tocher DR**, **Sargent JR**.

Institute of Aquaculture, University of Stirling, Stirling FK9 4LA, Scotland, U.K.

Duplicate groups of Atlantic salmon post-smolts were fed four purified diets supplemented with both vitamin E and the carotenoid astaxanthin (Ax) (+E, +Ax), or supplemented with either vitamin E or Ax (-E, +Ax and +E, -Ax) or deficient in both vitamin E and Ax (-E, -Ax) for 22 wk. There were no effects of diet on growth rate, but an extensive lipoid liver degenerative lesion was observed in 15% of fish fed diets deficient in vitamin E. Tissue vitamin E concentrations varied in accordance with dietary vitamin E in liver, muscle, heart, plasma, brain and eye; levels were reduced to approximately 3% in liver but only to 40% in eye of fish fed diets deficient in vitamin E compared with those fed diets supplemented with vitamin E. An interactive sparing of Ax supplementation on tissue vitamin E concentration was observed, but only in brain. Dietary deficiency of both vitamin E and Ax significantly increased the recovery of desaturated and elongated products of both [1-(14)C] 18:3(n-3) and [1-(14)C] 20:5(n-3) in isolated hepatocytes, suggesting that conversion of fatty acids to their long-chain highly unsaturated products can be stimulated by a deficiency of lipid-soluble antioxidants. The antioxidant synergism of vitamin E and Ax was supported by their ability to reduce malondialdehyde formation in an in vitro stimulation of microsomal lipid peroxidation and to reduce plasma levels of 8-isoprostane. The results of this study suggest that both vitamin E and the carotenoid Ax have antioxidant functions in Atlantic salmon.

Publication Types:

PMID: 10867054 [PubMed - indexed for MEDLINE]

Antioxidant

Biochim Biophys Acta. 2000 Jan 15;1463(1):179-87.

Exogenously incorporated ketocarotenoids in large unilamellar vesicles. Protective activity against peroxidation.

Rengel D, **Díez-Navajas A**, **Serna-Rico A**, **Veiga P**, **Muga A**, **Milicua JC**.

Department of Biochemistry and Molecular Biology, University of the Basque Country, P.O. Box 644, 48080, Bilbao, Spain.

The ability of astaxanthin and canthaxanthin as chain-breaking antioxidants was studied in Cu(2+)-initiated peroxidation of phosphatidylcholine large unilamellar vesicles (LUVs). Both carotenoids increased the lag period that precedes the maximum rate of lipid peroxidation, though astaxanthin showed stronger activity. For these experiments, different amounts of xanthophylls were exogenously added to previously made LUVs, non-incorporated pigment being afterwards removed. Differential scanning calorimetry assays with L-beta,gamma-dimyristoyl-alpha-phosphatidylcholine LUVs demonstrated that xanthophylls incorporated as described interact with the lipid matrix becoming interspersed among the phospholipid molecules.

Publication Types:

PMID: 10631307 [PubMed - indexed for MEDLINE]

Antioxidant

FEBS Lett. 1997 Nov 24;418(1-2):91-7.

Comparative mechanisms and rates of free radical scavenging by carotenoid antioxidants.

Mortensen A, **Skibsted LH**, **Sampson J**, **Rice-Evans C**, **Everett SA**.

Department of Dairy and Food Science, Royal Veterinary and Agricultural University, Frederiksberg C, Denmark.

The comparative mechanisms and relative rates of nitrogen dioxide (NO2.), thiyl (RS.) and sulphonyl (RSO2.) radical scavenging by the carotenoid antioxidants lycopene, lutein, zeaxanthin, astaxanthin and canthaxanthin have been determined by pulse radiolysis. All the carotenoids under study react with the NO2. radical via electron transfer to generate the carotenoid radical cation (Car.+). In marked contrast the glutathione and 2-mercaptoethanol thiyl radicals react via a radical addition process to generate carotenoid-thiyl radical adducts [RS-Car].. The RSO2. radical undergoes both radical addition, [RSO2-Car]. and electron abstraction, Car.+. Both carotenoid adduct radicals and radical cations decay bimolecularly. Absolute rate constants for radical scavenging were in the order of approximately 10(7)-10(9) M(-1) s(-1) and follow the sequence HO(CH2)2S. > RSO2. > GS. > NO2.. Although there were some discernible trends in carotenoid reactivity for individual radicals, rate constants varied by no greater than a factor of 2.5. The mechanism and rate of scavenging is strongly dependent on the nature of the oxidising radical species but much less dependent on the carotenoid structure.

Publication Types:

PMID: 9414102 [PubMed - indexed for MEDLINE]

Antioxidant

J Nutr Sci Vitaminol (Tokyo). 1997 Jun;43(3):345-55.

Inhibition of beta-carotene and astaxanthin of NADPH-dependent microsomal phospholipid peroxidation.

Nakagawa K, **Kang SD**, **Park DK**, **Handelman GJ**, **Miyazawa T**.

Department of Applied Biological Chemistry, Tohoku University, Sendai, Japan.

To evaluate the antioxidant effects of beta-carotene and astaxanthin, rat liver microsomes were exposed to a mixture of chelated iron (Fe3+/ADP) and NADPH. The carotenoids (190 pmol/mg protein) were incorporated into some of these microsomal membranes, and phospholipid hydroperoxides (PLOOH), thiobarbituric acid reactive substances (TBARS) and endogenous alpha-tocopherol content were measured over time after the initiation of oxidant stress. In control microsomes, oxidant stress led to accumulation of 1,865 (+/- 371) pmol PLOOH/mg protein during the initial 10-min peroxidation reaction, followed by a more gradual decrease during the subsequent 20-min of reaction. PLOOH accumulation during the initial 10-min reaction period was reduced to 588 (+/- 169) pmol/mg protein with beta-carotene present and 800 (+/- 288) pmol/mg protein with astaxanthin present. During the following 20-min of incubation, PLOOH levels declined in the carotenoid-supplemented microsomes but continued to increase at a slower rate in control preparations. TBARS did not show such large accumulation as observed in PLOOH during the initial 10-min incubation in any microsomal sample. The presence of carotenoids in the microsomal membrane partially inhibited the loss of alpha-tocopherol, especially during the later phase of oxidant stress. When lipid peroxidation is generated by membrane-bound cyt-P450, the specific measurement of PLOOH clearly demonstrates that the presence of carotenoids provides antioxidant protection.

PMID: 9268922 [PubMed - indexed for MEDLINE]

Z Lebensm Unters Forsch. 1993 May;196(5):423-9.

Carotenoid scavenging of radicals. Effect of carotenoid structure and oxygen partial pressure on antioxidative activity.

Jørgensen K, **Skibsted LH**.

RVAU Centre for Food Research, Royal Veterinary and Agricultural University, Frederiksberg, Denmark.

Carotenoid scavenging of free radicals has been investigated in peroxidizing methyl esters of unsaturated fatty acids using (i) metmyoglobin as a water-based free-radical initiator in a heterogeneous lipid/water system, and (ii) azo-bis-isobutyronitrile as a free-radical initiator in a homogeneous chloroform solution. For the heterogeneous system, using a combination of electrochemical oxygen depletion measurements, spectrophotometric determination of lipid hydroperoxides and carotenoid degradation, it was demonstrated that each of the four carotenoids astaxanthin, beta-carotene, canthaxanthin, and zeaxanthin protects the methyl esters against oxidation. The antioxidative effect increases with increasing carotenoid concentration, increases with decreasing oxygen partial pressure ($0.010 < pO2 < 0.50$ atm), and shows little dependence on the structure of the carotenoid. For a homogeneous solution, the effect of the structure of the carotenoid was further investigated, and it was shown that the stability of the four carotenoids in the oxidizing system are different, with the order of decreasing stability being: astaxanthin > canthaxanthin > beta-carotene > zeaxanthin. Each of the four carotenoids can suppress lipid oxidation and the degree of suppression of peroxidation of methyl linoleate corresponds to the difference in stability.

PMID: 8511974 [PubMed - indexed for MEDLINE]

Arch Biochem Biophys. 1992 Sep;297(2):291-5.

Astaxanthin and canthaxanthin are potent antioxidants in a membrane model.

Palozza P, **Krinsky NI**.

Department of Biochemistry, Tufts University School of Medicine, Boston, Massachusetts 02111-1837.

When the conjugated keto-carotenoids, either astaxanthin or canthaxanthin, are added to rat liver microsomes undergoing radical-initiated lipid peroxidation under air, they are as effective as alpha-tocopherol in inhibiting this process. This contrasts with the effect of beta-carotene, which is a much less potent antioxidant when added in this system, without the addition of other antioxidants.

Publication Types:

PMID: 1497349 [PubMed - indexed for MEDLINE]

Antioxidant

Biochim Biophys Acta. 1992 Jun 22;1126(2):178-84.

Antioxidant activity of xanthophylls on peroxyl radical-mediated phospholipid peroxidation.

Lim BP, **Nagao A**, **Terao J**, **Tanaka K**, **Suzuki T**, **Takama K**.

National Food Research Institute, Ministry of Agriculture, Forestry and Fisheries, Ibaraki, Japan.

The ability of xanthophylls (canthaxanthin, zeaxanthin, and astaxanthin) as chain-breaking antioxidants was investigated in peroxyl radical-mediated peroxidation of phosphatidylcholine (PC) liposomes under atmospheric conditions using lipid-soluble and water-soluble radical generators. These xanthophylls retarded the chain propagation reaction of phosphatidylcholine hydroperoxides (PC-OOH) formation, although their activities to trap chain-carrying peroxyl radical were much less than that of alpha-tocopherol. In chick plasma studies, it was observed that endogenious xanthophylls participated in the antioxidant defenses against the attack of aqueous peroxyl radical. It was concluded that xanthophylls possess the ability to act as chain-breaking antioxidants in the peroxidation of membraneous phospholipids. Dietary xanthophylls may, therefore, be helpful in resisting membraneous phospholipids against oxidative damage in vivo.

PMID: 1627620 [PubMed - indexed for MEDLINE]

Physiol Chem Phys Med NMR. 1990;22(1):27-38.

Inhibition of oxidative injury of biological membranes by astaxanthin.

Kurashige M, **Okimasu E**, **Inoue M**, **Utsumi K**.

Department of Medical Biology, Kochi Medical School, Japan.

The value of astaxanthin, a carotenoid pigment, in the treatment of oxidative injury is assessed. Astaxanthin protects the mitochondria of vitamin E-deficient rats from damage by Fe2(+)-catalyzed lipid peroxidation both in vivo and in vitro. The inhibitory effect of astaxanthin on mitochondrial lipid peroxidation is stronger than that of alpha-tocopherol. Thin layer chromatographic analysis shows that the change in phospholipid components of erythrocytes from vitamin E-deficient rats induced by Fe2+ and Fe3(+)-xanthine/xanthine oxidase system was significantly suppressed by astaxanthin. Carrageenan-induced inflammation of the paw is also significantly inhibited by administration of astaxanthin. These data indicate that astaxanthin functions as a potent antioxidant both in vivo and in vitro.

PMID: 2084711 [PubMed - indexed for MEDLINE]

Antioxidant

Lipids. 1989 Jul;24(7):659-61.

Antioxidant activity of beta-carotene-related carotenoids in solution.

Terao J.

Research Institute for Food Science, Kyoto University, Uji, Kyoto 611, Japan.

The effect of the antioxidant activity of beta-carotene and related carotenoids on the free radical-oxidation of methyl linoleate in solution was examined by measuring the production of methyl linoleate hydroperoxides. Canthaxanthin and astaxanthin which possess oxo groups at the 4 and 4'-positions in the beta-ionone ring retarded the hydroperoxide formation more efficiently than beta-carotene and zeaxanthin which possess no oxo groups. The rates of autocatalytic oxidation of canthaxanthin and astaxanthin were also slower than those of beta-carotene and zeaxanthin. These results suggest that canthaxanthin and astaxanthin are more effective antioxidants than beta-carotene by stabilizing the trapped radicals.

Publication Types:

PMID: 2779372 [PubMed - indexed for MEDLINE]

Antioxidant

Critical Reviews in Food Science and Nutrition, 46:185–196 (2006)

Astaxanthin: A Review of its Chemistry and Applications

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Centro de Investigaci´on en Alimentaci´on y Desarrollo, A.C., P.O. Box 1735. Hermosillo, Sonora. M´exico. 83000

Astaxanthin is a carotenoid widely used in salmonid and crustacean aquaculture to provide the pink color characteristic of that species. This application has been well documented for over two decades and is currently the major market driver for the pigment. Additionally, astaxanthin also plays a key role as an intermediary in reproductive processes. Synthetic astaxanthin dominates the world market but recent interest in natural sources of the pigment has increased substantially. Common sources of natural astaxanthin are the green algae Haematococcus pluvialis, the red yeast, Phaffia rhodozyma, as well as crustacean byproducts. Astaxanthin possesses an unusual antioxidant activity which has caused a surge in the nutraceutical market for the encapsulated product. Also, health benefits such as cardiovascular disease prevention, immune system boosting, bioactivity against Helycobacter pylori, and cataract prevention, have been associated with astaxanthin consumption. Research on the health benefits of astaxanthin is very recent and has mostly been performed in vitro or at the pre-clinical level with humans. This paper reviews the current available evidence regarding astaxanthin chemistry and its potential beneficial effects in humans.

Antioxidant

Lebensm Unters Forsch (1993) 196: 423-429

Carotenoid Scavenging of Radicals
Effect of carotenoid structure and oxygen partial pressure on antioxidative activiy

Kevin Jorgensen and Leif H. Skibsted

Carotenoid scavenging of free radicals has been investigated in peroxidating methyl esters of unsaturated fatty acids using (i) metmyoglobin as a water-based free-radical initiator in a heterogeneous lipid/water system, and (ii) azo-*bis*-isobutyronitrile as a free-radical initiator homogeneous chloroform solution. For the heterogeneous system, using a combination of electrochemical oxygen depletion measurements, spectrophotometric determination of lipid hydroperoxides and carotenoid degradation, it was demonstrated that each of the four carotenoids astaxanthin, β-carotene, canthaxanthin, and zeaxanthin protects the methyl esters against oxidation. The antioxidant effect increases with increasing carotenoid concentration increases with decreasing oxygen partial pressure ($0.010 < 0.50$ atm), and shows little dependence on the structure of the carotenoid. For a homogeneous solution, the effect of the structure of the carotenoid was further investigated, and it was shown that the stability of the four carotenoids in the oxidizing system are different, with the order of decreasing stability being: astaxanthin > canthaxanthin > β-carotene > zeaxanthin. Each of the four carotenoids can suppress lipid oxidation and the degree of suppression of peroxidation of methyl linoleate corresponds to the difference in stability.

Antioxidant

Pure & Appl. Chem., Vol. 63, No. 1, pp. 141-146, 1991.
Printed in Great Britain.

Biological functions and activities of animal carotenoids

Wataru Miki

Astaxanthin, on of the dominant carotenoids in marine animals, showed both a strong quenching effect against singlet oxygen, and a strong scavenging effect against free radicals. These effects are considered to be defense mechanisms in the animals for attacking these active oxygen species. The activities of astaxanthin are approximately 10 times stronger than those of other carotenoids that were tested, namely zeaxanthin, lutein, tunaxanthin, canthaxanthin and β-carotene, and 100 times greater than those of a tocopherol. Astaxanthin also showed strong activity as an inhibitor of lipid peroxidation mediated by these active forms of oxygen. From these results, astaxanthin has a the properties of a "SUPER VITAMIN E".

Antioxidant

Am J Cardiol 2008;101[suppl]:20D–29D

Biologic Activity of Carotenoids Related to Distinct Membrane Physicochemical Interactions

Hyesun McNulty, PhD,[a] Robert F. Jacob, PhD,[a] and R. Preston Mason, PhD[a,b,]*

Carotenoids are naturally occurring organic pigments that are believed to have therapeutic benefit in treating cardiovascular disease (CVD) because of their antioxidant properties. However, prospective randomized trials have failed to demonstrate a consistent benefit for the carotenoid _-carotene in patients at risk for CVD. The basis for this apparent paradox is not well understood but may be attributed to the distinct antioxidant properties of various carotenoids resulting from their structure-dependent physicochemical interactions with biologic membranes. To test this hypothesis, we measured the effects of astaxanthin, zeaxanthin, lutein, _-carotene, and lycopene on lipid peroxidation using model membranes enriched with polyunsaturated fatty acids. The correlative effects of these compounds on membrane structure were determined using small-angle x-ray diffraction approaches. The nonpolar carotenoids, lycopene and _-carotene, disordered the membrane bilayer and stimulated membrane lipid peroxidation (>85% increase in lipid hydroperoxide levels), whereas astaxanthin (a polar carotenoid) preserved membrane structure and exhibited significant antioxidant activity (>40% decrease in lipid hydroperoxide levels). These results suggest that the antioxidant potential of carotenoids is dependent on their distinct membrane lipid interactions. This relation of structure and function may explain the differences in biologic activity reported for various carotenoids, with important therapeutic implications.

Antioxidant

Int. J. Vitam. Nutr. Res., 77(1), 2007, 3-11

Effects pf Astaxanthin Supplementation on Lipid Peroxidation

Jouni Karppi, Tiina H. Rissanen, kristiina Nyyssonen, Jari Kaikkonen, Anders G. Olsson, Sari Voutilainen and Jukka T. Salonen

Abstract: Astaxanthin, the main carotenoid pigment in aquatic animals, has greater antioxidant activity *in vitro* (protecting against lipid peroxidation) and aa more polar configuration then 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 evaluate. The intervention group received two 4-mg astaxanthin (Astxan®) capsules daily, and the control group two identical-looking placebo capsules. Astaxanthin supplementation elevated plasma astaxanthin levels to 0.032 μmol/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, 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.

Antioxidant

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.

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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 Fe2+ and 2 mM H2O2. 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

Antioxidant

Reprod Domest Anim. 2009 Nov 18. [Epub ahead of print]

Antioxidative Effects of Astaxanthin against Nitric Oxide-Induced Oxidative Stress on Cell Viability and Gene Expression in Bovine Oviduct Epithelial Cell and the Developmental Competence of Bovine IVM/IVF Embryos.

Jang HY, Ji SJ, Kim YH, Lee HY, Shin JS, Cheong HT, Kim JT, Park IC, Kong HS, Park CK, Yang BK.

College of Animal Life Science, Kangwon National University, Chuncheon, Korea.

Abstract

Contents The aim of the present study was to elucidate the fundamental mechanism of bovine oviduct epithelial cell (BOEC) co-culture on developmental capacity of bovine in vitro oocyte maturation/in vitro fertilization (IVM/IVF) embryos. We examined the effects of astaxanthin against nitric oxide-induced oxidative stress on cell viability by MTT assay, lipid peroxidation (LPO) by using thiobarbituric acid (TBA) reaction for malondialdehyde (MDA) and the expression of antioxidant genes (CuZnSOD, MnSOD and Catalase) or apoptosis genes (Bcl-2, Caspase-3 and Bax) by RT-PCR in BOEC. We also evaluated the developmental rates of bovine IVM/IVF embryos co-cultured with BOEC pre-treated with astaxanthin (500 mum) in the presence or absence of sodium nitroprusside (SNP, 1000 mum) for 24 h. Cell viability in BOEC treated with SNP (50-2000 mum) lowered, while astaxanthin addition (50-500 mum) increased it in a dose-dependent manner. Cell viability in astaxanthin plus SNP (1000 mum) gradually recovered according to the increase in astaxanthin additions (100-500 mm). The LPO in astaxanthin group (50-500 muM) gradually decreased in a dose dependent manner and among SNP or astaxanthin plus SNP group, SNP alone and astaxanthin (50 muM) plus SNP shown a significant increase than other groups ($p < 0.05$). Expression of apoptosis or antioxidant genes was detected by RT-PCR. Bcl-2 and antioxidant genes were detected in astaxanthin or astaxanthin plus SNP group, and Caspase-3 and Bax genes were only found in SNP group. When bovine IVM/IVF embryos were cultured for 6-7 days under co-culture system such as BOEC treated with astaxanthin in the presence or absence of SNP, the developmental ability to blastocysts in 500 mum astaxanthin group was the highest of all groups. These results suggest that astaxanthin has a antioxidative effect on cell viability and LPO of BOEC, and development of bovine IVM/IVF embryos due to the induction of antioxidant genes and suppression of apoptosis genes.

PMID: 19930137 [PubMed - as supplied by publisher]

Antioxidant

Cell Biol Toxicol. 2010 Oct;26(5):457-67. Epub 2010 Mar 14.

Astaxanthin prevents in vitro auto-oxidative injury in human lymphocytes.

Bolin AP, Macedo RC, Marin DP, Barros MP, Otton R.

Cellular Physiology Laboratory, Postgraduate Program-Health Science, CBS, Cruzeiro do Sul University, Tatuapé, São Paulo, Brazil.

Abstract

Upon mitogen sensitization, lymphocytes undergo proliferation by oxyradical-based mechanisms. Through continuous resting-restimulation cycles, lymphocytes accumulate auto-induced oxidative lesions which lead to cell dysfunction and limit their viability. Astaxanthin (ASTA) is a nutritional carotenoid that shows notable antioxidant properties. This study aims to evaluate whether the in vitro ASTA treatment can limit oxyradical production and auto-oxidative injury in human lymphocytes. Activated lymphocytes treated with 5 microM ASTA showed immediate lower rates of O(2)(*-) /H(2)O(2) production whilst NO* and intracellular Ca(2+) levels were concomitantly enhanced (<or=4 h). In long-term treatments (>24 h), the cytotoxicity test for ASTA showed a sigmoidal dose-response curve (LC50 = 11.67 +/- 0.42 microM), whereas higher activities of superoxide dismutase and catalase in 5 microM ASTA-treated lymphocytes were associated to significant lower indexes of oxidative injury. On the other hand, lower proliferative scores of ASTA lymphocytes might be a result of diminished intracellular levels of pivotal redox signaling molecules, such as H(2)O(2). Further studies are necessary to establish the ASTA-dose compensation point between minimizing oxidative damages and allowing efficient redox-mediated immune functions, such as proliferation, adhesion, and oxidative burst.

PMID: 20229275 [PubMed - in process]

Antioxidant

Eur J Nutr. 2010 Apr 2. [Epub ahead of print]

Astaxanthin addition improves human neutrophils function: in vitro study.

Macedo RC, Bolin AP, Marin DP, Otton R.

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Tatuapé, São Paulo, SP, CEP 03342-000, Brazil.

Abstract

PURPOSE: The aim of the present study was to evaluate the in vitro effect of carotenoid astaxanthin (ASTA) on the phagocytic and microbicidal capacities, cytokine release, and reactive oxygen species production in human neutrophils.
METHODS: The following parameters were evaluated: cytotoxic effect of ASTA on human neutrophils viability, phagocytic and microbicidal capacities of neutrophils by using Candida albicans assay, intracellular calcium mobilization (Fura 2-AM fluorescent probe), superoxide anion (lucigenin and DHE probes), hydrogen peroxide (H(2)O(2), phenol red), and nitric oxide (NO.) (Griess reagent) production, activities of antioxidant enzymes (total/Mn-SOD, CAT, GPx, and GR), oxidative damages in biomolecules (TBARS assay and carbonyl groups), and cytokine (IL-6 and TNF-alpha) release.
RESULTS: Astaxanthin significantly improves neutrophil phagocytic and microbicidal capacity, and increases the intracellular calcium concentration and NO. production. Both functional parameters were accompanied by a decrease in superoxide anion and hydrogen peroxide and IL-6 and TNF-alpha production. Oxidative damages in lipids and proteins were significantly decreased after ASTA-treatment.
CONCLUSIONS: Taken together our results are supportive to a beneficial effect of astaxanthin-treatment on human neutrophils function as demonstrated by increased phagocytic and fungicide capacity as well as by the reduced superoxide anion and hydrogen peroxide production, however, without affecting neutrophils capacity to kill C. albicans. This process appears to be mediated by calcium released from intracellular storages as well as nitric oxide production.

PMID: 20361333 [PubMed - as supplied by publisher]

Antioxidant

Phytother Res. 2010 Jan;24(1):54-9.

Cytoprotective role of astaxanthin against glycated protein/iron chelate-induced toxicity in human umbilical vein endothelial cells.

Nishigaki I, Rajendran P, Venugopal R, Ekambaram G, Sakthisekaran D, Nishigaki Y.

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Abstract

Astaxanthin (ASX), a red carotenoid pigment with no pro-vitamin A activity, is a biological antioxidant that occurs naturally in a wide variety of plants, algae and seafoods. This study investigated whether ASX could inhibit glycated protein/iron chelate-induced toxicity in human umbilical-vein endothelial cells (HUVEC) by interfering with ROS generation in these cells. Glycated fetal bovine serum (GFBS) was prepared by incubating fetal bovine serum (FBS) with high-concentration glucose. Stimulation of cultured HUVECs with 50 mm 1 mL of GFBS significantly enhanced lipid peroxidation and decreased antioxidant enzyme activities and levels of phase II enzymes. However, preincubation of the cultures with ASX resulted in a marked decrease in the level of lipid peroxide (LPO) and an increase in the levels of antioxidant enzymes in an ASX concentration-dependent manner. These results demonstrate that ASX could inhibit LPO formation and enhance the antioxidant enzyme status in GFBS/iron chelate-exposed endothelial cells by suppressing ROS generation, thereby limiting the effects of the AGE-RAGE interaction. The results indicate that ASX could have a beneficial role against glycated protein/iron chelate-induced toxicity by preventing lipid and protein oxidation and increasing the activity of antioxidant enzymes.

PMID: 19548280 [PubMed - indexed for MEDLINE]

Antioxidant

Anti-Inflammatory

Mol Cells. 2003 Aug 31;16(1):97-105.

Astaxanthin inhibits nitric oxide production and inflammatory gene expression by suppressing I(kappa)B kinase-dependent NF-kappaB activation.

Lee SJ, **Bai SK**, **Lee KS**, **Namkoong S**, **Na HJ**, **Ha KS**, **Han JA**, **Yim SV**, **Chang K**, **Kwon YG**, **Lee SK**, **Kim YM**.

Vascular System Research Center and Department of Molecular and Cellular Biochemistry, Kangwon National University Biology, Chunchon 200-701, Korea.

Astaxanthin, a carotenoid without vitamin A activity, has shown anti-oxidant and anti-inflammatory activities; however, its molecular action and mechanism have not been elucidated. We examined in vitro and in vivo regulatory function of astaxanthin on production of nitric oxide (NO) and prostaglandin E2 (PGE2) as well as expression of inducible NO synthase (iNOS), cyclooxygenase-2, tumor necrosis factor-alpha (TNF-alpha), and interleukin-1beta (IL-1beta). Astaxanthin inhibited the expression or formation production of these proinflammatory mediators and cytokines in both lipopolysaccharide (LPS)-stimulated RAW264.7 cells and primary macrophages. Astaxanthin also suppressed the serum levels of NO, PGE2, TNF-alpha, and IL-1beta in LPS-administrated mice, and inhibited NF-kappaB activation as well as iNOS promoter activity in RAW264.7 cells stimulated with LPS. This compound directly inhibited the intracellular accumulation of reactive oxygen species in LPS-stimulated RAW264.7 cells as well as H2O2-induced NF-kappaB activation and iNOS expression. Moreover, astaxanthin blocked nuclear translocation of NF-kappaB p65 subunit and I(kappa)B(alpha) degradation, which correlated with its inhibitory effect on I(kappa)B kinase (IKK) activity. These results suggest that astaxanthin, probably due to its antioxidant activity, inhibits the production of inflammatory mediators by blocking NF-kappaB activation and as a consequent suppression of IKK activity and I(kappa)B-alpha degradation.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 14503852 [PubMed - indexed for MEDLINE]

J Microbiol Biotechnol. 2008 Dec;18(12):1990-6.

Effects of astaxanthin on the production of NO and the expression of COX-2 and iNOS in LPS-stimulated BV2 microglial cells.

Choi SK, **Park YS**, **Choi DK**, **Chang HI**.

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Astaxanthin has shown antioxidant, antitumor, and antiinflammatory activities; however, its molecular action and mechanism in the nervous system have yet to be elucidated. We examined the in vitro effects of astaxanthin on the production of nitric oxide (NO), as well as the expression of inducible NO synthase (iNOS) and cyclooxygenase-2 (COX-2) in lipopolysaccharide (LPS)-stimulated BV2 microglial cells. Astaxanthin inhibited the expression or formation of nitric oxide (NO), iNOS and COX-2 in lipopolysaccharide (LPS)-stimulated BV-2 microglial cells. Astaxanthin also suppressed the protein levels of iNOS and COX-2 in LPS-stimulated BV2 microglial cells. These results suggest that astaxanthin, probably due to its antioxidant activity, inhibits the production of inflammatory mediators by blocking iNOS and COX-2 activation or by the suppression of iNOS and COX-2 degradation.

PMID: 19131704 [PubMed - in process]

Anti-Inflammatory

Biol Pharm Bull. 2004 Feb;27(2):170-3.

Evaluation of the nitric oxide radical scavenging activity of manganese complexes of curcumin and its derivative.

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Curcumin manganese complex (CpCpx) and diacetylcurcumin manganese complex (AcylCpCpx) were determined as to their effect on the nitric oxide (NO) radical scavenging in vitro method using a sodium nitroprusside generating NO system compared with their parent compound and astaxanthin, an extreme antioxidant. All compounds effectively reduced the generation of NO radicals in a dose dependent manner. They exhibited strong NO radical scavenging activity with low IC(50) values. The IC(50) values of curcumin, diacetylcurcumin, CpCpx and AcylCpCpx obtained are 20.39+/-4.10 microM, 28.76+/-1.48 microM, 9.79+/-1.50 microM and 8.09+/-0.99 microM, respectively. CpCpx and AcylCpCpx show greater NO radical scavenging than their parent compounds, curcumin and acetylcurcumin, respectively. However, the IC(50) values of curcumin and related compounds were found to be less than astaxanthin, an extreme antioxidant, with the lower IC(50) value of 3.42+/-0.50 microM.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 14758027 [PubMed - indexed for MEDLINE]

Anti-Inflammatory

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

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

Ohgami K, **Shiratori K**, **Kotake S**, **Nishida T**, **Mizuki N**, **Yazawa K**, **Ohno S**.

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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.

Publication Types:

- Comparative Study
- Research Support, Non-U.S. Gov't

PMID: 12766075 [PubMed - indexed for MEDLINE]

Anti-Inflammatory

Trends Biotechnol. 2003 May;21(5):210-6.

Haematococcus astaxanthin: applications for human health and nutrition.

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The carotenoid pigment astaxanthin has important applications in the nutraceutical, cosmetics, food and feed industries. Haematococcus pluvialis is the richest source of natural astaxanthin and is now cultivated at industrial scale. Astaxanthin is a strong coloring agent and a potent antioxidant - its strong antioxidant activity points to its potential to target several health conditions. This article covers the antioxidant, UV-light protection, anti-inflammatory and other properties of astaxanthin and its possible role in many human health problems. The research reviewed supports the assumption that protecting body tissues from oxidative damage with daily ingestion of natural astaxanthin might be a practical and beneficial strategy in health management.

Publication Types:

- Review

PMID: 12727382 [PubMed - indexed for MEDLINE]

Anti-Inflammatory

EFFECT OF AN ASTAXANTHIN-CONTAINING PRODUCT ON CARPAL TUNNEL SYNDROME

Nir, Y., Spiller, G., Multz, C.
Health Research and Studies Center, Los Altos, CA,
Study Report, May, 2002

ABSTRACT

Carpal Tunnel Syndrome (CTS) is a debilitating disease often requiring surgery. Because not all patients respond to surgery and current non-surgical treatments provide limited benefits, investigations into alternative techniques are necessary. We investigated the effect of an extract of *Haematococcus* algae grown in Hawaii, taken three times a day, each dose supplying 4 mg of astaxanthin, 40 ug lutein, 65 IU vitamin A as beta-carotene, and 50 IU of vitamin E, on the symptoms of CTS in a double-blind, placebo-controlled, parallel design study. Twenty participants were randomized to receive either the extract (13 subjects) or a placebo (7 subjects) for eight weeks. Daytime pain rate and duration were measured at the beginning of the study, and after 4 and 8 weeks of treatment, with the use of questionnaires. Results showing a trend towards decreasing pain rate and duration in the subjects receiving the extract, but because of the small number of subjects the results did not reach statistical significance ($P>0.05$). The daytime pain rates (mean ± SD) at 0, 4 and 8 weeks were, respectively, 1.69±0.99, 1.23±0.70, and 1.00±0.88 for the treatment group, and 1.67±0.47, 1.83±0.37, and 1.50±0.50 for the control group. Similarly, the duration of daytime pain was 2.15±1.23, 1.69±1.13, and 1.38±1.44 for the treatment group, and 2.17± 1.07, 2.67± 1.10, and 2.17± 1.34 for the control group. The positive trend observed in this pilot study suggests that an astaxanthin-containing product may be effective in treating symptoms of CTS. Further investigations in a larger-scale study are needed.

Supported by a grant from the Cyanotech Corporation

Anti-Inflammatory

Effect of daily use natural astaxanthin on C-reactive protein.

Gene A. Spiller, PhD, Antonella Dewell, MS, RD, Sally Chaves, RN, Zaga Rakidzich
Health Research & Studies Center, Los Altos, CA
Study Report, January, 2006

ABSTRACT
Previous studies have provided data suggesting that daily use of natural astaxanthin can positively address inflammatory conditions such as rheumatoid arthritis and carpal tunnel syndrome. In this study, the effect of daily use of BioAstin™, a microalgae extract containing natural astaxanthin, on C-reactive protein was evaluated. It was found that after daily use of BioAstin for eight weeks C-reactive protein (CRP) was significantly lowered in the treatment group as compared to the placebo group. This correlation of reduced CRP and use of BioAstin™ may suggest that daily use can help reduce CRP and possibly lower inflammation levels in the body.

Supported by a grant from the Cyanotech Corporation

Anti-Inflammatory

ASTAXANTHIN SUPPLEMENTATION

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Abstract

PURPOSE: To determine the effects of astaxanthin anti-oxidant supplementation as a counter-measure for delayed onset muscular soreness (DOMS) in currently trained individuals, nine weight trained males (X±SE: age=25.1±1.6 yrs., hgt=1.79±0.02 m, wgt=86.8±4.4 kg) participated in this study. **METHODS**: All subjects provided muscle biopsy samples from the vastus lateralis m. prior to inducing DOMS in the knee extensor mm. (10 sets x 7-10 reps, 85% eccentric 1 RM). The subjects ingested either 4 mg.d-1 of astaxanthin (Suppl; n=4) or a placebo (Con; n=5) for a 3 week loading phase prior to the DOMS-inducing protocol, and during a 12 d recovery phase. Perceptions of DOMS at 48 hrs post-eccentric exercise were quantified by muscle soreness ratings (0-10 Likert scale). Muscle fiber characteristics were determined via mATPase histochemistry and digital imaging to determine % cross-sectional areas of the major fiber types (I, IIA, IIAB/B). Due to small numbers of IIB fibers in some subjects, IIAB hybrid fibers were included in this fiber type population. Simple regression was used to determine relationships between fiber characteristics and perceptions of soreness. **RESULTS**: No differences in perceptions of soreness between the Suppl or Con groups were observed ($p>0.05$), with all subjects exhibiting a mean score of >5. Percent fiber type areas were similar ($p>0.05$) for both groups (type I, Suppl=47.6±8.9%, Con=41.3±2.7%; type IIA, Suppl=44.3±5.6%, Con=53.0±2.8%; type IIAB/B, Suppl=8.2±3.6%, Con=5.7±1.6%). However, 48 hrs after the DOMS-inducing session, perceptions of soreness for the Suppl group were positively related to % area type I ($r=0.90$), and negatively related to % area types IIA ($r=-0.80$) and IIAB/B ($r=-0.99$). A distinctly different correlational pattern was observed for the Con group (% type I area, $r=-0.58$; % type IIA area, $r=0.32$; % type IIAB/B area, $r=0.40$). **CONCLUSIONS**: Collectively, these preliminary data suggest that astaxanthin supplementation may preferentially attenuate perceptions of DOMS in weight trained men with a high % area for fiber types IIA & AB/B.

Supported by a grant from the Cyanotech Corporation

Effect of Astaxanthin on Muscular Atrophy

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Objective: Patients wearing casts or other devices that hinder mobility are reported to have muscular atrophy. It is commonly thought that the cause is from reactive oxygen species (ROS). The use of Vitamin E, along with other antioxidants, prevents ROS from causing muscular atrophy that arises from lack of movement; however there has been conflicting reports. In this experiment, Astaxanthin (Ax), which is considered to be a more effective antioxidant than Vitamin E or beta-carotene, will be administered to subjects as food supplement to see its effect on muscular atrophy caused by lack of movement. It will also be tested if the amount of Ax intake will make a difference in its effectiveness. Methods: 14-week old, Wister-type, male rats were used. Mice were all the same weight after growth for one week under controlled conditions. The rats were separated into three separate groups: Control group (n=7), Ax 0.04% group, and Ax 0.2% group. 15 days after the administration of Ax, each rat had his right leg contained with a cast in an extended position to decrease muscle mass in the triceps surae muscle group for 10 days. At the end of the experiment, the weights of the rats were measured and, along with the use of Nembutal (an anesthesia), euthanized. The plantaris muscle was extracted for analysis.

Results and Analysis: Groups that were administered Ax had significantly less muscle atrophy than those in the Control group ($p<0.05$). The level of Cu/Zn-SOD expressed was higher in the rats with casts than those without casts in the control group; however, in the Ax group, the level expressed was insignificantly different from those with casts and those without. In addition, the level expressed in the control group with casts was significantly higher than the Ax group with casts on. The level of calpain and ubiquitin expressed was higher in the control group with casts than those in the Ax group with casts, but the difference was insignificant. Also, significantly less (of calpain and ubiquitin) was expressed in the Ax 0.2% with casts compared to the control group with casts. The same pattern was seen with Capthesin L expression.
Presently, it is reported that muscular atrophy in patients who are immobile due to casts was caused by oxidative stress. The increase in oxidative stress accelerates the reaction of lipoperoxide, which causes distress in the cell membrane and sarcoendoplaxmic reticulum, leading to an increase in Ca2+ in the cytoplasm and concurrently causing a decrease in its discharge. An increase in Ca2+ concentration activates calpain along with cathepsin. In addition, the presence of lipoperoxide causes disruption in the cell membrane of the mitrocondria, causing iron ions and ROS to leak in the cytoplasm, which leads to ubiquitination (of proteins.) Ax is the same as beta-carotene in that they are both carotenoids. They both prevent lipoperoxides from disturbing the cell membrane in many biological organisms, but Ax is more active than other antioxidants. Based on

this information, we believe Ax intake prevents muscular atrophy by protecting membranes; preventing oxidative stress which results in atrophy; preventing the facilitation protease and ubiquitination. The effects due to the quantity of Ax uptake were not clear in this study.

Anti-Inflammatory

Long term dietary antioxidant intakes attenuate sarcopenia

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Oxidative stress is thought to be one of significant contributing factors to age-related sarccpenia. We tested the hypothesis that the long term dietary antioxidant (astaxanthinl intakes attenuate sarcopenie. Wistar strain male rats, aged 45 weeks old, were given either control (Cont) or astaxanthin feed (0.004%, Ax) for 1 year. 'The soleus muscle weights and muscle weigh-to-body weight ratios in Ax group were significantly heavier than in Cont group, but tibialis anterior muscle mass remained similar between the two dietary groups. The level of ubiquitinated proteins was significantly lower in soleus muscles of Ax group, but not in tibialis anterior muscles when compared with Cont group. Tibialis anterior levels of cathepsin Land caepase-S were tended to be lower in Ax group than in Cont group, especially significant differences observed in cathepsin L, whereas no differences between Cont and Ax were observed in soleus tbcae levels. There woro no effects ofAx supplementation on calpaia 1 and 2, UBC3B, CulZn SOD and nitrotyrosine levels inboth soleus and tibialis anterior muscles. OUT data suggest that the long term dietary astaxanthin intakes attenuate the age related muscle atrophy, due in part, to reductions in oxidative stress and ubiquitination of myofibrillar protein in slow soleus muscles, but not in fast tibialis anterior muscles.

EFFECT OF AN ASTAXANTHIN-CONTAINING PRODUCT ON RHEUMATOID ARTHRITIS

Nir, Y., Spiller, G., Multz, C.
Health Research and Studies Center, Los Altos, CA
Study Report, May 2002

ABSTRACT

Rheumatoid arthritis (RA) is a chronic destructive disorder requiring aggressive treatment. Conventional treatments present problems in terms of safety and efficacy, and the alternative therapies so far investigated have not yielded consistent results. We investigated the effect of an extract of *Haematococcus* algae grown in Hawaii, taken three times a day, each dose supplying 4 mg of astaxanthin, 40 ug lutein, 65 IU vitamin A as beta-carotene, and 50 IU of vitamin E, on the symptoms of RA in a double-blind, placebo-controlled, parallel design study. Twenty-one subjects were randomized to receive either the extract (14 subjects) or a placebo (7 subjects) for eight weeks. Pain and satisfaction with the ability to perform daily activities were measured at the beginning of the study, and after 4 and 8 weeks of treatment. The results showed a significant difference ($P<0.05$) both in pain and satisfaction scores between the treatment and control groups at the end of the study. Pain scores (mean±SD, VAS scale) at 0, 4, and 8 weeks were respectively, 0.42±0.22, 0.38±0.21, and 0.27±0.25 for the treatment group, and 0.48±0.23, 0.42±0.16, and 0.45±0.14 for the control group. Satisfaction scores were 1.75±0.72, 1.50±0.76, and 1.00±0.60 for the treatment group, and 1.83±0.69, 1.50±0.96, and 1.67±0.94 for the control group. Astaxanthin-based supplements appear to be an effective addition in the treatment of RA and further studies should be carried out with a larger population.

Supported by a grant from the Cyanotech Corporation

Anti-Inflammatory

Effect of daily use of natural astaxanthin on symptoms associated with Tennis Elbow (lateral humeral epicondylitis)

Gene A. Spiller, PhD, CNS, Antonella Dewell, MS, RD, Sally Chaves, RN, Zaga Rakidzich,
Health Research & Studies Center, Los Altos, CA
Study Report, January, 2006

ABSTRACT
Previous studies have provided data suggesting that daily use of a microalgal extract containing natural astaxanthin and marketed under the trade name BioAstin® can help alleviate pain associated with joint damage, specifically that seen in rheumatoid arthritis and carpal tunnel syndrome. For this study, the benefits of daily use natural astaxanthin provided by BioAstin® for the purpose of alleviating pain associated with Tennis Elbow (lateral humeral epicondylitis) was evaluated. It was found that grip strength measurements (GSM) for those on the active product were significantly improved by the end of the study. This correlation of improved GSM and use of natural astaxanthin may suggest that daily use can help alleviate pain associated with Tennis Elbow, and increase mobility. This improvement may greatly improve the standard of living for those who suffer from such joint disorders.

Supported by a grant from the Cyanotech Corporation

Anti-Inflammatory

Am J Cardiol 2008;101[suppl]:58D– 68D

Astaxanthin: A Novel Potential Treatment for Oxidative Stress and Inflammation in Cardiovascular Disease

Fredric J. Pashkow, MD,[a,b,]* David G. Watumull,[b] and Charles L. Campbell, MD[c]

Oxidative stress and inflammation are implicated in several different manifestationsof cardiovascular disease (CVD). They are generated, in part, from the overproduction of reactive oxygen species (ROS) and reactive nitrogen species (RNS) thatactivate transcriptional messengers, such as nuclear factor–_B, tangibly contributing to endothelial dysfunction, the initiation and progression of atherosclerosis, irreversible damage after ischemic reperfusion, and even arrhythmia, such as atrial fibrillation. Despite this connection between oxidative stress and CVD, there are currently no recognized therapeutic interventions to address this important unmet need. Antioxidants that provide a broad, "upstream" approach via ROS/RNS quenching or free radical chain breaking seem an appropriate therapeutic option based on epidemiologic, dietary, and in vivo animal model data. However, human clinical trials with several different well-known agents, such as vitamin E and _-carotene, have been disappointing. Does this mean antioxidants as a class are ineffective, or rather that the "right" compound(s) have yet to be found, their mechanisms of action understood, and their appropriate targeting and dosages determined? A large class of potent naturally-occurring antioxidants exploited by nature—the oxygenated carotenoids (xanthophylls)— have demonstrated utility in their natural form but have eluded development as successful targeted therapeutic agents up to the present time. This article characterizes the mechanism by which this novel group of antioxidants function and reviews their preclinical development. Results from multiple species support the antioxidant/anti-inflammatory properties of the prototype compound, astaxanthin, establishing it as an appropriate candidate for development as a therapeutic agent for cardiovascular oxidative stress and inflammation.

Phytother Res. 2010 Jul 14. [Epub ahead of print]

Summative interaction between astaxanthin, Ginkgo biloba extract (EGb761) and vitamin C in Suppression of respiratory inflammation: a comparison with ibuprofen.

Haines DD, Varga B, Bak I, Juhasz B, Mahmoud FF, Kalantari H, Gesztelyi R, Lekli I, Czompa A, Tosaki A.

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Abstract

In this study, combinations of Ginkgo biloba leaf extract (EGb761) plus the carotenoid antioxidant astaxanthin (ASX) and vitamin C were evaluated for a summative dose effect in the inhibition of asthma-associated inflammation in asthmatic guinea-pigs. Ovalbumin-sensitized Hartley guinea-pigs challenged with ovalbumin aerosol to induce asthma, were administered EGb761, ASX, vitamin C or ibuprofen. Following killing, bronchoalveolar lavage (BAL) fluid was evaluated for inflammatory cell infiltrates and lung tissue cyclic nucleotide content. Each parameter measured was significantly altered to a greater degree by drug combinations, than by each component acting independently. An optimal combination was identified that included astaxanthin (10 mg/kg), vitamin C (200 mg/kg) and EGb761 (10 mg/kg), resulting in counts of eosinophils and neutrophils each 1.6-fold lower; macrophages 1.8-fold lower, cAMP 1.4-fold higher; and cGMP 2.04-fold higher than levels in untreated, asthmatic animals ($p < 0.05$). In conclusion, EGb761, ASX and vitamin C are shown here to interact summatively to suppress inflammation with efficacy equal to or better than ibuprofen, a widely used non-steroidal antiinflammatory drug (NSAID). Such combinations of non-toxic phytochemicals constitute powerful tools for the prevention of onset of acute and chronic inflammatory disease if consumed regularly by healthy individuals; and may also augment the effectiveness of therapy for those with established illness. Copyright (c) 2010 John Wiley & Sons, Ltd.

PMID: 20632299 [PubMed - as supplied by publisher]

Skin Health

Exp Dermatol. 2009 Mar;18(3):222-31. Epub 2008 Sep 18.

Astaxanthin, canthaxanthin and beta-carotene differently affect UVA-induced oxidative damage and expression of oxidative stress-responsive enzymes.

Camera E, **Mastrofrancesco A**, **Fabbri C**, **Daubrawa F**, **Picardo M**, **Sies H**, **Stahl W**.

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Carotenoids are used for systemic photoprotection in humans. Regarding mechanisms underlying photoprotective effects of carotenoids, here we compared the modulation of UVA-related injury by carotenoids. Human dermal fibroblasts (HDF) were exposed to moderate doses of UVA, which stimulated apoptosis, increased levels of reactive oxygen species and thiobarbituric acid reactive substances, decreased antioxidant enzymes activities, promoted membrane perturbation, and induced the expression of heme oxygenase-1 (HO-1). The carotenoids astaxanthin (AX), canthaxanthin (CX) and beta-carotene (betaC) were delivered to HDF 24 h before exposure to UVA. Astaxanthin exhibited a pronounced photoprotective effect and counteracted all of the above-mentioned UVA-induced alterations to a significant extent. beta-Carotene only partially prevented the UVA-induced decline of catalase and superoxide dismutase activities, but it increased membrane damage and stimulated HO-1 expression. Moreover, betaC dose-dependently induced caspase-3 activity following UVA exposure. In contrast, CX had no effect on oxidative damage, except for HO-1 expression, which was augmented. Uptake of AX by fibroblasts was higher than that of the other two carotenoids. The photostability of the three compounds in fibroblasts was AX > CX >> betaC. The data indicate that the oxo-carotenoid AX has a superior preventive effect towards photo-oxidative changes in cell culture.

Publication Types:

PMID: 18803658 [PubMed - in process]

J Dermatol Sci. 2002 Oct;30(1):73-84.

Modulatory effects of an algal extract containing astaxanthin on UVA-irradiated cells in culture.

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UV radiation from sunlight is the most potent environmental risk factor in skin cancer pathogenesis. In the present study the ability of an algal extract to protect against UVA-induced DNA alterations was examined in human skin fibroblasts (1BR-3), human melanocytes (HEMAc) and human intestinal CaCo-2 cells. The protective effects of the proprietary algal extract, which contained a high level of the carotenoid astaxanthin, were compared with synthetic astaxanthin. DNA damage was assessed using the single cell gel electrophoresis or comet assay. In 1BR-3 cells, synthetic astaxanthin prevented UVA-induced DNA damage at all concentrations (10 nM, 100 nM, 10 microM) tested. In addition, the synthetic carotenoid also prevented DNA damage in both the HEMAc and CaCo-2 cells. The algal extract displayed protection against UVA-induced DNA damage when the equivalent of 10 microM astaxanthin was added to all three-cell types, however, at the lower concentrations (10 and 100 nM) no significant protection was evident. There was a 4.6-fold increase in astaxanthin content of CaCo-2 cells exposed to the synthetic compound and a 2.5-fold increase in cells exposed to algal extract. In 1BR-3 cells, exposure to UVA for 2 h resulted in a significant induction of cellular superoxide dismutase (SOD) activity, coupled with a marked decrease in cellular glutathione (GSH) content. However pre-incubation (18 h) with 10 microM of the either the synthetic astaxanthin or the algal extract prevented UVA-induced alterations in SOD activity and GSH content. Similarly, in CaCo-2 cells a significant depletion of GSH was observed following UVA-irradiation which was prevented by simultaneously incubating with 10 microM of either synthetic astaxanthin or the algal extract. SOD activity was unchanged following UVA exposure in the intestinal cell line. This work suggests a role for the algal extract as a potentially beneficial antioxidant.

Publication Types:

PMID: 12354422 [PubMed - indexed for MEDLINE]

Skin Health

J Dermatol Sci. 1998 Mar;16(3):226-30.

Modulation of UVA light-induced oxidative stress by beta-carotene, lutein and astaxanthin in cultured fibroblasts.

O'Connor I, **O'Brien N**.

Department of Nutrition, University College, Cork, Ireland.

The ability of beta-carotene, lutein or astaxanthin to protect against UVA-induced oxidative stress in rat kidney fibroblasts (NRK) was assessed. Activities of the antioxidant enzymes catalase (CAT) and superoxide dismutase (SOD), and changes in thiobarbituric acid reactive substances (TBARS) were measured as indices of oxidative stress. Exposure to UVA light at a dose intensity of 5.6 mW/cm2 for 4 h resulted in a significant decrease in CAT and SOD activities and a significant increase in TBARS. No cytotoxicity, as indicated by lactate dehydrogenase (LDH) release, was observed. beta-Carotene (1 microM), lutein (1 microM) and astaxanthin (10 nM) protect against UVA light-induced oxidative stress in vitro with astaxanthin exhibiting superior protective properties.

Publication Types:

PMID: 9651820 [PubMed - indexed for MEDLINE]

Int J Vitam Nutr Res. 1995;65(2):79-86.

Vitamin A status and metabolism of cutaneous polyamines in the hairless mouse after UV irradiation: action of beta-carotene and astaxanthin.

Savouré N, Briand G, Amory-Touz MC, Combre A, Maudet M, Nicol M.

Biochimie Médicale A - Faculté de Médecine de Rennes, France.

Solar radiations (UV A and B) can cause epidermis photoaging and skin cancers. These frequently irreversible effects result from the in situ generation of free radicals. However, it has been noted that nutritional factors can modulate photochemical damage, in particular the common carotenoids present in food, which can be considered as potential prophylactic agents against carcinogenesis. We investigated the effect of UV A and B radiations on the skin of the SKH1 hairless mouse fed a diet either lacking in vitamin A or supplemented with retinol, beta-carotene or astaxanthin. The latter is an oxygenated carotenoid (like canthaxanthin) without provitamin A activity and with strong singlet oxygen quenching ability. After analysing of vitamin status of each group (plasma retinol concentrations and hepatic reserves), we searched for UV-induced modifications of polyamine metabolism by measuring epidermal ornithine decarboxylase (ODC) activity and free polyamines concentration (putrescine, spermidine and spermine). In the basal state without irradiation, differences in ODC activity between groups were nonsignificant; but after UV stimulation, ODC increased markedly in the skin of vitamin A-deficient animals, much more than in other groups. Curiously, the addition of astaxanthin or beta-carotene to the regimen containing retinol reduced the protective effect of retinol alone. Regarding polyamines after irradiation, putrescine was significantly increased in the skin of deficient animals, in parallel with ODC activity. However, astaxanthin had a stronger inhibitory effect on putrescine accumulation than retinol, and decreased spermidine and spermine concentrations: this suggests a specific action on transglutaminases.

Publication Types:

PMID: 7591536 [PubMed - indexed for MEDLINE]

Beauty From Within: A Synergistic Combination Of Astaxanthin And Tocotrienol For Beauty Supplements

Yamashita, E.

(2002) Cosmetic Benefit of Dietary Supplements Containing Astaxanthin and Tocotrienol on Human Skin. Food Style 21 6(6):112-17.

Previously reported dermatological benefits of natural astaxanthin included anti-hyperpigmentation, melanin synthesis inhibition, and reduced photo-skin aging. Hence, the potency of astaxanthin for cosmetic effect is "clearly visible". Another class of natural compounds called tocotrienols also offer cosmetic benefits. A member of the vitamin E family, its isomeric form (chemically identical, but structurally different) imparts greater protection against free radicals than its popular cousin, alpha-tocopherol. Tocotrienols are generally 40-60 times more powerful than alpha-tocopherols in terms of free radical protection. Both astaxanthin and tocotrienols are found naturally in daily foods we consume. By concentrating these into an oral beauty supplement, it can provide an excellent source of protection in addition to the daily skincare regime. Results in 4 weeks supplementation indicated reduction in fine wrinkles, increased skin moisture and increased skin elasticity compared to placebo.

(Adapted from Nutrition Business Journal, December 2004)

Beauty clinical: Astaxanthin with Omega 3 and Marine Glycosaminoglycans

Alain Thibodeau, Director of Scientific Affairs for Atrium Biotechnologies Inc. in Quebec, Canada published results of a blinded parallel group clinical trial on topical and supplemental forms of a product they call MRT2 (Matrix Rejuvenation Technology 2). The trial was done using both a topical product containing marine glycosaminoglycans and a supplement containing marine glycosaminoglycans, astaxanthin and omega-3 fatty acids. The trial involved 100 subjects.

Significant improvements were measured in skin hydration and elasticity. Skin appearance (including skin tone, fine lines and sallowness) also showed benefits, with the strongest improvements made in subjects using both the supplement and the topical products.

"We can demonstrate a synergistic activity between the topical product and the dietary supplement…The topical product works. The supplement works as well, but you get much better results from using both" said Thibodeau.

Cosmetics.! Toiletries"'magazine/57 VOL lIS, No. l/January2003 57-9

Dietary /Nutritional Supplements: The New Allyto TopicalCosmetic Formulations?

Alain Thibodeau and Edouard lauzler

Dietary/Nutritional Supplements

Dietary/nutritional supplements can be used to make active nutrients available to all organs of the body. As mentioned earlier, skin is an organ and may therefore benefit from active nutrients conveyed by dietary/nutritional supplements. The repercussions of nutrient on skin health are well exemplified by the fact that some skin disorders are directly linked to nutritional deficiencies.

Conversely, skin plays a major role in maintaining bone health through the synthesis of vitamin D. the interrelation between skin and the nutritional homeostasis has been recently highlighted and calls upon the understanding of the cellular and molecular processes in play.

We have performed a clinical trail in which a topical cream formulation and a dietary/nutritional supplement were concomitantly administered. The dietary/nutritional supplement provided proteoglycans, collagen, glucosamine, carotenoid pigment (astaxanthin esters) and omega-3 essential fatty acids (EPA and DHA). The efficacy of this regimen was demonstrated on the visual appearance of signs of aging as well as by the amelioration of functional properties of the skin.

Skin Health

Journal of Cosmetic Dermatology Volume 4 Page 277 - December 2005

A novel micronutrient supplement in skin aging: a randomized placebo-controlled double-blind study

Alain Béguin

Summary
Background: Skin aging, a combination of intrinsic and environmentally induced processes, predominantly ultraviolet (UV) light from the sun, results in characteristic tissue alterations, such as the degradation of collagen and the formation of visible fine lines and wrinkles.
Objective To test the efficacy and safety of a novel micronutrient supplement (Estime® containing BioAstin Natural Astaxanthin) in skin aging.
Methods A 4-month randomized double-blind controlled study including 40 subjects where the supplement was tested against placebo for 3 months followed by a 1-month supplement-free period for both groups to assess lasting effects. Efficacy measurements included skin surface evaluation, ultrasound measurement of sun-exposed and protected areas of the skin (back of the hand and ventral forearms, respectively), and photographic assessment.
Results All investigated parameters showed a continuous and significant improvement in the active group during the 3 months of supplementation as compared to placebo. Photographs showed visible improvement of the overall skin appearance and reduction of fine lines. Ultrasound measurements showed an increase in dermis density of up to 78% in the active group ($P < 0.0001$). The final assessment after 1 month without supplementation showed no further improvements, but a slight decrease was observed in most improved parameters. No treatment-related side effects were reported.
Conclusion The study demonstrated that the supplement appears to be effective and safe as an oral supplement to protect the skin and support its repair process. Recommendations are made for further evaluations.

Carotenoid Science Vol 10, p 91-5 (2006)

The Effects of a Dietary Supplement Containing Astaxanthin on Skin Condition

Eiji Yamashita

The somatic effect son human skin by 4mg per day astaxanthin supplementation were demonstrated in a single blind placebo controlled study using forty-nine US healthy middle-aged woman. There were significant improvements in fine lines/wrinkles and elasticity by dermatologist's assessment and in the moisture content by instrumental assessment at week 6 compares to base-line initial values.

Astaxanthin, widely and naturally distributed in marine organisms, including Crustacea such as shrimps and crabs and such fish as salmon and sea bream exhibits a strong anti-oxidative effect, and its action is reported to 1,000 times stronger then alpha-tocopherol and approximately 40 times stronger than beta-carotene. It has also been reported that astaxanthin doesn't have any pro-oxidative nature like beta-carotene and lycopene and its potent anti-oxidant property is exhibited at the cell membrane. Although used only as a coloring in the past (either as a food additive or a dye-up agent for cultured fish), astaxanthin has become one of the major materials eagerly anticipated by industries for dietary supplements and personal care products.

Furthermore its other various important benefits to date have suggested fro human health such as anti-inflammation, LDL cholesterol oxidation suppression, immunomodulation, anti-stress, limiting diabetic nephropathy, improved semen quality, attenuating eye fatigue, sport performance and endurance, limiting exercised induced muscle damage and improving hypertension.

In terms of dermatolofical actions, suppression of hyper-pigmentation, inhibitions of melanin synthesis and photo-aging have been reported. We have also reported visual wrinkled reduction by topical astaxanthin. However, only one study for internal use about cosmetic benefit of a dietary supplement including astaxanthin and tocotrienol on human skin has been reported.

Here we report the effects of a dietary supplement containing astaxanthin on skin condition performed in the United States of America.

Fragr J VOL.34;NO.3;PAGE.21-27(2006)

Biological activities of astaxanthin and its cosmeceutical application.

YAMASHITA EIJI

The present review covers cosmeceutical benefits of astaxanthin that is one of the most abundant carotenoids in nature, particularly in marine based life. The anti-oxidant properties of astaxanthin without any pro-oxidative nature working at cell membrane and cosmeceutical effects such as anti-hyperpigmentation, anti-photoaging, melanin inhibition and visual wrinkle reduction by topical or internal use and one of the action mechanisms of astaxanthin on NF-kB dependent inflammation are introduced. And current and future cosmeceutical applications of astaxanthin particularly from a green microalgae Haematococcus pluvialis that is the most ideal source in the earth are discussed describing actual examples of astaxanthin containing skin care products in Japanese market.

Photoprotective Effect of Astaxanthin Applied to the Skin

Arakane, K. 2002. KOSE Corporation

Reactive oxygen species generated by exposing the skin to sunlight are responsible for sunburn, lipid peroxidation and degenerative changes in dermal connective tissues. This causes premature aging of the skin.

A researcher from a Japanese company called KOSE Corporation compared astaxanthin to other commonly used ingredients in cosmetics that are thought to protect the skin from the damaging effects of sunlight. He found that astaxanthin potentially offers greater antioxidant protection against premature signs of aging.

Carotenoid Science, Vol. 5, p21-4 April 2002 Toyama, Japan

Superior Skin Protection via Astaxanthin

Kumi Arakane

It has been believed for a long time that the skin exists only for the purpose of merely protecting our body by physically shielding it from outside factors. But in recent years, along with the radical progress in the field of dermatological science studies, it is known that the skin does actually indicate various responses and accept acute and chronic damages under UV irradiation. According to the enthusiastic studies to clarify the mechanism leading to the skin damages, nowadays the reactive oxygen species generated by UV irradiation is considered to be an important factor mediating photo-induced skin damages. Accumulation skin damages by reactive oxygen species such' as lipid peroxidation, sunburn and degenerative changes in dermal connective tissues induce the skin aging. To protect skin from reactive oxygen species, many cosmetics contain nowadays both naturally occurring molecules and synthetic compounds as antioxidant However. B-carotene was the only carotenoid for cosmetics among more than 600 carotenoids which had been isolated from nature, until astaxanthin from Antarctic krill was approved for cosmetics in 1997. In this paper, I would like to show the possibility of astaxanthin as a cosmetic ingredient and the useful formula for maintaining the stability of astaxanthin in the preparation.

Journal of Japanese Cosmetic Science Society VOL.29;NO.1;PAGE.9-19(2005)

Preventive Effects of Carotenoids on Photoaging and Its Application for Cosmetics

MIZUTANI YUKI; SAKATA OSAMU; HOSHINO TAKU; HONDA YOSHIKO; YAMASHITA MIKA; ARAKANE KUMI; SUZUKI TADASHI

Carotenoids are functional materials and more than 650 kinds of carotenoides are isolated from nature. They have been applied for foods, but most of these carotenoids have not been studied in terms of their effects on skin functions, and because of their instability under light exposure they were hardly used in the cosmetics field until now. Using hairless mice irradiated with UVB to produce photoaged skin, we investigated the inhibitory effect of astaxanthin on wrinkle formation, decrease of skin elasticity, ultrastructural change of dermal collagen fiber bundles and elastic fibers and the level of matrix metalloproteinase-1 (MMP-1) activity. These results indicated that the astaxanthin had the superior protection effect on photoaging as a ROS scavenger. It is well known that carotenoids are easy to decompose during storage by UV light and oxygen. We found that the incorporation of dl-.ALPHA.-tocopherol and .ALPHA.-glucosyl rutin was able to maintain long-term stability of astaxanthin in preparation. This research demonstrated the superior anti-aging effects by carotenoids and this is the first time for carotenoids to be practically applicable to cosmetic formulation.

Fragr J VOL.29;NO.12;PAGE.98-103(2001)

Effects of astaxanthin from Haematococcus pluvialis on human skin. Patch testing Skin repeated application test Effect on wrinkle reduction.

SEKI TAISUKE; SUEKI HIROHIKO; KONO HIROMI; SUGANUMA KAORU; YAMASHITA EIJI

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 H. 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.

Journal of Japanese Cosmetic Science Society VOL.27;NO.4;PAGE.298-303(2003)

Effect of Antioxidant to Inhibit UV-Induced Wrinkles

ARAKANE KUMI

Living organisms are protected from harmful ultraviolet (UV) rays by the ozone layer surrounding the earth. However, depletion of the ozone layer and an increase in the amount of UV rays in sunlight reaching the earth's surface have been recently reported. As a result, social concerns over the effects of UV on living organisms have been increasing year by year. The skin covers the outer surface of the body, and so it is most vulnerable to UV. Because UV-induced wrinkles are prominently observed only in sun-exposed areas, they are apparently caused by chronic damage due to accumulated UV exposure. In addition to a change in appearance (large deep wrinkles), histological changes including thickening of the epidermis and dermis, elastin fiber deposition and decreased collagen fibers are observed as a result of continuous UV irradiation. Many reports indicate the involvement of action of reactive oxygen species in UV-induced wrinkles formation. Reactive oxygen species are known to damage essential elements including collagen and elastin which maintain elasticity and firmness of the skin, and also damage the function of fibroblasts producing these elements. It goes without saying that application of UV-absorbing agents is effective in preventing changes associated with photoaging. It is also reported that antioxidants such as vitamins C, E and iron chelators are effective for photoaging. We demonstrate that reactive oxygen species quenchers play an important role in reduction of UV-induced wrinkles formation using a carotenoid, astaxanthin, which has no pro-vitamin A activity unlike .BETA.-carotene, and a new iron chelator, N-(4-pyridoxylmethylene)-L-serine (PYSer), which consists of biomimetic molecules and effectively suppresses production of hydroxyl radical by chelating iron in skin. The demonstrable and potential roles of antioxidants for suppression of UV-induced wrinkles formation effectively are summarized here.

J Dermatol Sci. 2010 May;58(2):136-42. Epub 2010 Feb 18.

Astaxanthin attenuates the UVA-induced up-regulation of matrix-metalloproteinase-1 and skin fibroblast elastase in human dermal fibroblasts.

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Abstract

BACKGROUND: Repetitive exposure of the skin to UVA radiation elicits sagging more frequently than wrinkling, which is mainly attributed to its biochemical mechanism to up-regulate the expression of matrix-metalloproteinase (MMP)-1 and skin fibroblast elastase (SFE)/neutral endopeptidase (NEP), respectively. OBJECTIVE: In this study, we examined the effects of a potent antioxidant, astaxanthin (AX), on the induction of MMP-1 and SFE by UVA treatment of cultured human dermal fibroblasts. METHODS: Those effects were assessed by real-time RT-PCR, Western blotting and enzymic activity assays. RESULTS: UVA radiation elicited a significant increase in the gene expression of MMP-1 as well as SFE/NEP (to a lesser extent) which was followed by distinct increases in their protein and enzymatic activity levels. The addition of AX at concentrations of 4-8 microM immediately after UVA exposure significantly attenuated the induction of MMP-1 and SFE/NEP expression elicited by UVA at the gene, protein and activity levels although both the UVA stimulation and the subsequent AX inhibition were greater for MMP-1 than for SFE/NEP. Analysis of the UVA-induced release of cytokines revealed that UVA significantly stimulated only the secretion of IL-6 among the cytokines tested and that AX significantly diminished only the IL-6 secretion. CONCLUSION: These findings indicate that, based on different effective concentrations of AX, a major mode of action leading to the inhibition elicited by AX depends on inhibition of UVA effects of the reactive oxygen species-directed signaling cascade, but not on interruption of the IL-6-mediated signaling cascade. We hypothesize that AX would have a significant benefit on protecting against UVA-induced skin photo-aging such as sagging and wrinkles. 2010 Japanese Society for Investigative Dermatology.

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Plant Physiol Biochem. 2008 Oct;46(10):875-83. Epub 2008 Jun 6.

Transgenic carrot plants accumulating ketocarotenoids show tolerance to UV and oxidative stresses.

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Ketocarotenoids are strong antioxidant compounds which accumulate in salmon, shrimp, crustaceans and algae, but are rarely found naturally in higher plants. In this study, we engineered constitutive expression of an algal beta-carotene ketolase gene (bkt) in carrot plants to produce a number of ketocarotenoids from beta-carotene. These included astaxanthin, adonirubin, canthaxanthin, echinenone, adonixanthin and beta-cryptoxanthin. Leaves accumulated up to 56 microg/g total ketocarotenoids and contained higher beta-carotene levels but lower levels of alpha-carotene and lutein. The photosynthetic capacity of transgenic plants was not significantly altered by these changes. However, when high-expressing transgenic plants were exposed to UV-B irradiation, they grew significantly better than the wild-type controls. Similarly, leaf tissues exposed to various oxidative stresses including treatment with H(2)O(2) and methyl viologen showed less injury and retained higher levels of chlorophyll a+b. Total carotenoid extracts from transgenic leaves had higher antioxidant and free-radical scavenging activity in vitro compared to control leaves. Transgenic tissues also accumulated lower amounts of H(2)O(2) following exposure to oxidative stresses, suggesting that free radical and reactive oxygen species were quenched by the ketocarotenoids.

Publication Types:

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Eye Health

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.

Journal of Clinical Therapeutics & Medicines VOL.22;NO.1;PAGE.41-54(2006)

The supplementation effect of Astaxanthin on Accommodation and Asthenopia

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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., "blear-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.

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.

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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 (H2O2) 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 H2O2 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(-1), 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.

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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**.

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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 chemotactic 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:

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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]

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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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Astaxanthin Interacts with Selenite and Attenuates Selenite-Induced Cataractogenesis.

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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 muM) 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.

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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.

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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 > 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.

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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.

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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:

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

Wu TH, **Liao JH**, **Hou WC**, **Huang FY**, **Maher TJ**, **Hu CC**.

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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 Fe2+ and 2 mM H2O2. 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:

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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**.

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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(-1)) 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(-1) 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:

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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.

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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(2) 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(2)-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]

Cataract formation in Atlantic salmon, Salmo salar L., smolt relative to dietary pro- and antioxidants and lipid level.

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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(-1)) and high levels (below known toxic levels and 320 g lipid kg(-1)). 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]

Journal of Clinical Therapeutics & Medicines VOL.21;NO.4;PAGE.431-436(2005)

Effects of Astaxanthin on Accommodative Recovery

TAKAHASHI NANAKO (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.

Journal of Traditional Medicines VOL.19;NO.5;PAGE.170-173(2002)

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.+-.1.5 diopters. Accommodation amplitudes (2.3.+-.1.4 and 2.2.+-.1.0 diopters) in Groups B and C before supplementation were significantly ($p<0.05$) lower than in Group A. Accommodation amplitude (2.8.+-.1.6 diopters) in Group B after astaxanthin treatment was significantly ($p<0.01$) larger than before supplementation, while accommodation amplitude (2.3.+-.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.+-.4.2Hz, 6.5+/=1.8.MU.V, and 101.3.+-.6.5msec, 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.

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

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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.

Bechettobyo ni kansuru Chosa Kenkyu Heisei 14 Nendo Sokatsu, Buntan Kenkyu Hokokusho VOL.;NO.;PAGE.98-99(2003)

Research on the anti-inflammatory effect of astaxanthin

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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.

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 (Tmax) in serum and iris/ciliary body was 9 hours (at Cmax 61.3 ng/mL) and 24 hours (at Cmax 79.3) respectively. In other human studies with oral intake of astaxanthin, the Tmax 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.

Patent No. 5,527,533. Washington, D.C., U.S. Patent and Trademark Office, June 18, 1996.

Method of Retarding and Ameliorating Central Nervous System and Eye Damage

Tso, Mark O. M., Lam, Tim-Tak

Current theory on diseases and injuries of the eye and central nervous system is that they are caused by the increased generation and presence of singlet oxygen and other free radicals (superoxide, hydroxyl, hydrogen peroxide, etc.) or by decreased removal ability. This includes but is not limited to age-related macular degeneration, the leading cause of blindness in the United States, retinal arterial and venous occlusion, glaucoma and diabetic retinopathy and injuries resulting from trauma and inflammation.

These free radicals are generated by continuous or excessive exposure to light and the highly oxygenated environment of the normal eye, ischemia (some form of blockage that deprives the eye of nutrition and oxygen) and reperfusion (the reoxygenation of tissue after blockage removal), and enzymatic processes. Free radicals oxidize the polyunsaturated fatty acids in the retina which leads to functional impairment of the retinal cell membranes, causing temporary and permanent damage to the retinal cells. Once the retina is damaged, it cannot be replaced. An antioxidant that can reach the inner eye by crossing the blood-brain and blood-retinal barriers would certainly afford the eye protection from these damaging conditions.

Astaxanthin is a carotenoid not found in the eye. Dr. Mark Tso first of all proved that astaxanthin could cross the blood-brain and blood-retinal barriers by feeding astaxanthin to rats and finding it in their eyes. He then proved it protected the eye from light-induced damage, photoreceptor cell damage, ganglion cell damage, neuronal damage and inflammatory damage. Dr. Tso fed rats either astaxanthin or placebo, exposed them to damaging light and then compared the thickness of their retinas to a normal eye. The astaxanthin retina was 42 micrometers thick, the placebo retina 32 micrometers thick and the normal retina 45 micrometers thick. Astaxanthin provided significant protection.

In the ischemia-reperfusion experiment, rats were fed either astaxanthin or placebo, exposed to highly elevated intraocular pressure (ischemia) for an hour and returned to normal pressure (reperfusion). After a week, the retinas of the astaxanthin-treated rats were about 70 micrometers while the placebo retinas were 62 micrometers (normal being 120 micrometers). Once again, this is statistically significant protection.

Not only did astaxanthin protect the photoreceptor cells but rhodopsin levels also and performed better than beta-carotene used in the same type of experiment. Astaxanthin also exerts a protective effect on the central nervous system in general.

Eye Health

Journal of the Eye VOL.23;NO.6;PAGE.829-834(2006)

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.

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.

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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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.

Journal of Clinical Therapeutics & Medicines VOL.18;NO.9;PAGE.1085-1100(2002)

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

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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.

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.

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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.

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 Fe2+ and 2 mM H2O2. 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.

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Neuroprotective

Forum Nutr. 2009;61:129-35. Epub 2009 Apr 7.

Astaxanthin protects neuronal cells against oxidative damage and is a potent candidate for brain food.

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Astaxanthin (AST) is a powerful antioxidant that occurs naturally in a wide variety of living organisms. Based on the report claiming that AST could cross the brain-blood barrier, the aim of this study was to investigate the neuroprotective effect of AST by using an oxidative stress-induced neuronal cell damage system. The treatment with DHA hydroperoxide (DHA-OOH) or 6-hydroxydopamine (6-OHDA), either of which is a reactive oxygen species (ROS)-inducing neurotoxin, led to a significant decrease in viable dopaminergic SH-SY5Y cells by the MTT assay, whereas a significant protection was shown when the cells were pretreated with AST. Moreover, 100 nM AST pretreatment significantly inhibited intracellular ROS generation that occurred in either DHA-OOH- or 6-OHDA-treated cells. The neuroprotective effect of AST is suggested to be dependent upon its antioxidant potential and mitochondria protection; therefore, it is strongly suggested that treatment with AST may be effective for oxidative stress-associated neurodegeneration and a potential candidate for natural brain food.

PMID: 19367117 [PubMed - in process]

FASEB J. 2009 Jun;23(6):1958-68. Epub 2009 Feb 13.

Astaxanthin reduces ischemic brain injury in adult rats.

Shen H, **Kuo CC**, **Chou J**, **Delvolve A**, **Jackson SN**, **Post J**, **Woods AS**, **Hoffer BJ**, **Wang Y**, **Harvey BK**.

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Astaxanthin (ATX) is a dietary carotenoid of crustaceans and fish that contributes to their coloration. Dietary ATX is important for development and survival of salmonids and crustaceans and has been shown to reduce cardiac ischemic injury in rodents. The purpose of this study was to examine whether ATX can protect against ischemic injury in the mammalian brain. Adult rats were injected intracerebroventricularly with ATX or vehicle prior to a 60-min middle cerebral artery occlusion (MCAo). ATX was present in the infarction area at 70-75 min after onset of MCAo. Treatment with ATX, compared to vehicle, increased locomotor activity in stroke rats and reduced cerebral infarction at 2 d after MCAo. To evaluate the protective mechanisms of ATX against stroke, brain tissues were assayed for free radical damage, apoptosis, and excitoxicity. ATX antagonized ischemia-mediated loss of aconitase activity and reduced glutamate release, lipid peroxidation, translocation of cytochrome c, and TUNEL labeling in the ischemic cortex. ATX did not alter physiological parameters, such as body temperature, brain temperature, cerebral blood flow, blood gases, blood pressure, and pH. Collectively, our data suggest that ATX can reduce ischemia-related injury in brain tissue through the inhibition of oxidative stress, reduction of glutamate release, and antiapoptosis. ATX may be clinically useful for patients vulnerable or prone to ischemic events.

Publication Types:

PMID: 19218497 [PubMed - indexed for MEDLINE]

PMCID: PMC2698661 [Available on 2010/06/01]

Neuroprotective

J Clin Biochem Nutr. 2009 May;44(3):280-4. Epub 2009 Apr 25.

Preliminary Clinical Evaluation of Toxicity and Efficacy of A New Astaxanthin-rich Haematococcus pluvialis Extract.

Satoh A, **Tsuji S**, **Okada Y**, **Murakami N**, **Urami M**, **Nakagawa K**, **Ishikura M**, **Katagiri M**, **Koga Y**, **Shirasawa T**.

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Astaxanthin (Ax), a carotenoid ubiquitously distributed in microorganisms, fish, and crustaceans, has been known to be a potent antioxidant and hence exhibit various physiological effects. We attempted in these studies to evaluate clinical toxicity and efficacy of long-term administration of a new Ax product, by measuring biochemical and hematological blood parameters and by analyzing brain function (using CogHealth and P300 measures). Ax-rich Haematococcus pluvialis extracts equivalent to 4, 8, 20 mg of Ax dialcohol were administered to 73, 38, and 16 healthy adult volunteers, respectively, once daily for 4 weeks to evaluate safety. Ten subjects with age-related forgetfulness received an extract equivalent to 12 mg in a daily dosing regimen for 12 weeks to evaluate efficacy. As a result, no abnormality was observed and efficacy for age-related decline in cognitive and psychomotor functions was suggested.

PMID: 19430618 [PubMed - in process]

PMCID: PMC2675019

Neuroprotective

Brain Res. 2009 Feb 13;1254:18-27. Epub 2008 Dec 3.

Astaxanthin inhibits reactive oxygen species-mediated cellular toxicity in dopaminergic SH-SY5Y cells via mitochondria-targeted protective mechanism.

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Astaxanthin is a powerful antioxidant that occurs naturally in a wide variety of living organisms. The aim of this study is to investigate the effect and the mechanism of astaxanthin on reactive oxygen species (ROS)-mediated apoptosis in dopaminergic SH-SY5Y cells. The treatment with DHA hydroperoxide (DHA-OOH) or 6-hydroxydopamine (6-OHDA), either of which is ROS-inducing neurotoxin, led to a significant decrease in viable dopaminergic SH-SY5Y cells by MTT assay, whereas a significant protection was shown while the cells were pretreated with astaxanthin. Moreover, 100 nM astaxanthin pretreatment significantly inhibited apoptosis, mitochondrial abnormalities and intracellular ROS generation occurred in either DHA-OOH- or 6-OHDA-treated cells. The neuroprotective effect of astaxanthin is suggested to be dependent upon its antioxidant potential and mitochondria protection; therefore, it is suggested that astaxanthin may be an effective treatment for oxidative stress-associated neurodegeneration.

PMID: 19101523 [PubMed - indexed for MEDLINE]

Neuroprotective

J Neurochem. 2008 Dec;107(6):1730-40. Epub 2008 Nov 7.

Protective effects of astaxanthin on 6-hydroxydopamine-induced apoptosis in human neuroblastoma SH-SY5Y cells.

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Parkinson's disease (PD) is a neurodegenerative disorder characterized by selective loss of dopaminergic neurons in the substantia nigra pars compacta. Although understanding of the pathogenesis of PD remains incomplete, increasing evidence from human and animal studies has suggested that oxidative stress is an important mediator in its pathogenesis. Astaxanthin (Asx), a potent antioxidant, has been thought to provide health benefits by decreasing the risk of oxidative stress-related diseases. This study examined the protective effects of Asx on 6-hydroxydopamine (6-OHDA)-induced apoptosis in the human neuroblastoma cell line SH-SY5Y. Pre-treatment of SH-SY5Y cells with Asx suppressed 6-OHDA-induced apoptosis in a dose-dependent manner. In addition, Asx strikingly inhibited 6-OHDA-induced mitochondrial dysfunctions, including lowered membrane potential and the cleavage of caspase 9, caspase 3, and poly(ADP-ribose) polymerase. In western blot analysis, 6-OHDA activated p38 MAPK, c-jun NH(2)-terminal kinase 1/2, and extracellular signal-regulated kinase 1/2, while Asx blocked the phosphorylation of p38 MAPK but not c-jun NH(2)-terminal kinase 1/2 and extracellular signal-regulated kinase 1/2. Pharmacological approaches showed that the activation of p38 MAPK has a critical role in 6-OHDA-induced mitochondrial dysfunctions and apoptosis. Furthermore, Asx markedly abolished 6-OHDA-induced reactive oxygen species generation, which resulted in the blockade of p38 MAPK activation and apoptosis induced by 6-OHDA treatment. Taken together, the present results indicated that the protective effects of Asx on apoptosis in SH-SY5Y cells may be, at least in part, attributable to the its potent antioxidative ability.

Publication Types:

PMID: 19014378 [PubMed - indexed for MEDLINE]

Neuroprotective

Alcohol Clin Exp Res. 2008 Aug;32(8):1417-21. Epub 2008 Jun 6.

Dose-dependent effects of astaxanthin on cortical spreading depression in chronically ethanol-treated adult rats.

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BACKGROUND: The consumption of alcoholic drinks is a frequent drug-abuse situation, which is associated to a wide variety of pathological disturbances affecting several organs, including the brain. We have previously shown in the developing rat brain that ethanol intake facilitates the propagation of cortical spreading depression (CSD), an excitability-related neural phenomenon present in several animal species. This electrophysiological effect was attenuated by a shrimp (Litopenaeus vannamei) carotenoids extract. Here we investigated the effects of pure astaxanthin, the main carotenoid found in shrimp, on CSD. METHODS: Adult Wistar rats were treated per gavage, during 18 days, with 2.5, 10 or 90 microg/kg/d astaxanthin dissolved in ethanol (3 g/kg) and CSD was recorded on the cortical surface 1 to 3 days thereafter. Four groups, treated respectively with ethanol, distilled water and soybean oil with- and without astaxanthin were also studied for comparison with the ethanol + astaxanthin groups. RESULTS: Ethanol-treated rats displayed higher CSD-velocities (mean values, in mm/min, per hour of recording ranging from 4.08 +/- 0.09 to 4.12 +/- 0.16), compared to the distilled water-group (from 3.19 +/- 0.13 to 3.27 +/- 0.06). Addition of astaxanthin to ethanol lead to lower CSD-velocities in a dose-dependent manner, ranging from 3.68 +/- 0.09 to 3.97 +/- 0.22 for the 2.5 microg/kg/d-dose, from 3.29 +/- 0.09 to 3.32 +/- 0.07 for the 10 microg/kg/d-dose, and from 2.89 +/- 0.13 to 2.92 +/- 0.11 for the 90 microg/kg/d-dose. The velocities of the soybean oil groups (with and without astaxanthin) were not statistically different from the 10 microg/kg/d astaxanthin + ethanol and distilled water groups. CONCLUSION: The results demonstrate the antagonistic effect of astaxanthin against the ethanol-induced facilitation of CSD propagation. Probably carotenoid antioxidant properties are involved in such effects.

Publication Types:

PMID: 18540920 [PubMed - indexed for MEDLINE]

Neuroprotective

Environ Geochem Health. 2007 Dec;29(6):483-9. Epub 2007 Aug 25.

Impact of astaxanthin-enriched algal powder of Haematococcus pluvialis on memory improvement in BALB/c mice.

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The impact of astaxanthin-enriched algal powder on auxiliary memory improvement was assessed in BALB/c mice pre-supplemented with different dosages of cracked green algal (Haematococcus pluvialis) powder daily for 30 days. The supplemented mice were first tested over 8 days to find a hidden platform by swimming in a Morris water maze. Then, for 5 days, the mice were used to search for a visible platform in a Morris water maze. After that, the mice practised finding a safe place--an insulated platform in a chamber--for 2 days. During these animal experimental periods, similar algal meals containing astaxanthin at 0, 0.26, 1.3 and 6.4 mg/kg body weight were continuously fed to each group of tested mice. Profiles of latency, distance, speed and the direction angle to the platforms as well as the diving frequency in each group were measured and analyzed. The process of mice jumping up onto the insulated platform and diving down to the copper-shuttered bottom with a 36 V electrical charge were also monitored by automatic video recording. The results of the Morris maze experiment showed that middle dosage of H. pluvialis meals (1.3 mg astaxanthin/kg body weight) significantly shortened the latency and distance required for mice to find a hidden platform. However, there was no obvious change in swim velocity in any of the supplemented groups. In contrast, the visible platform test showed a significant increase in latency and swim distance, and a significant decrease in swim speed for all groups of mice orally supplemented with H. pluvialis powder compared to the placebo group ($P < 0.05$ or $P < 0.01$). Mice supplemented with the algal meal hesitantly turned around the original hidden platform, in contract to mice supplemented with placebo, who easily forgot the original location and accepted the visible platform as a new safe place. These results illustrate that astaxanthin-enriched H. pluvialis powder has the auxiliary property of memory improvement. The results from the platform diving test showed that the low and middle dosage of H. pluvialis powder, rather that the high dosage, increased the latency and reduced the frequency of diving from the safe insulated platform to the electrically stimulated copper shutter, especially in the low treatment group ($P < 0.05$). These results indicate that H. pluvialis powder is associated with dose-dependent memory improvement and that a low dosage of algal powder (<or=middle treatment group) is really good for improving the memory.

PMID: 17721823 [PubMed - indexed for MEDLINE]

Neuroprotective

Effects of astaxanthin on brain damages due to ischemia

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Brain requires high energy-supply to keep its normal function. Well-developed blood vessels in the brain supply enough glucose and oxygen to generate required energy. When some part of blood vessels were closed or occluded by some reason, the area supported by those blood vessels will fall into ischemia and the neuronal cells distributed in the area will be damaged or die. Since neuronal cells have no neogenetic properties, the functions supported by the area will be lost forever. We know and take care of large scale of neuronal cell death which will cause severe loss of brain function, but we ignore small scale of ischemia which may have no apparent dysfunction. However senile dementia will be formed due to the accumulation of such small scale ischemic neuronal cell death. Although big efforts have been made to develop some drugs to rescue the cells exposed to ischemia from death, we have no effective drugs so far. Since astaxanthin has been known to have antioxidant effects, we expected this drug to rescue the cell damage during ischemia and re-perfusion.

In the present study we used slice preparations (300 urn) of hippocampus obtained from young adult rats. To measure intracellular Ca2+ concentration before, during and after ischemia we stained the slice preparation by fura-z, a Ca2+ indicator. The fluorescence of loaded fura-S was analyzed by an image processor (Argus 50;Hamamatsu photonics). To examine brain edema during ischemia we used self-made devise, which is consisted of an infra-red differential interferance microscope with an infra-red camera and an image processor and measured" contrast value" as indices ofedema. Astaxanthin (0.003%)pretreated for ten minutes before ischemia reduced the increase in intracellular Ca2+ concentration duirng ischemia and accelerate the recoveryfrom the abnormal increase in Ca2+ concentration Preteated astaxantin (0.01%)alsoreduced the edema developedduring ischemia

Although present results were still preliminary, astaxanthin can be expected to have effective rescuing effects on neuronal damages induced by ischemia.

Neuroprotective

January 2005 Biol. Pharm. Bull. 28(1) 47—52 (2005) 47

Antihypertensive and Neuroprotective Effects of Astaxanthin in Experimental Animals

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Received May 18, 2004; accepted October 5, 2004

Astaxanthin is a natural antioxidant carotenoid that occurs in a wide variety of living organisms. We investigated, for the first time, antihypertensive effects of astaxanthin (ASX-O) in spontaneously hypertensive rats (SHR). Oral administration of ASX-O for 14 d induced a significant reduction in the arterial blood pressure (BP) in SHR but not in normotensive Wistar Kyoto (WKY) strain. The long-term administration of ASX-O (50 mg/kg) for 5 weeks in stroke prone SHR (SHR-SP) induced a significant reduction in the BP. It also delayed the incidence of stroke in the SHR-SP. To investigate the action mechanism of ASX-O, the effects on PGF2a-induced contractions of rat aorta treated with NG-nitro-l-arginine methyl ester (L-NAME) were studied in vitro. ASX-O (1 to 10mM) induced vasorelaxation mediated by nitric oxide (NO). The results suggest that the antihypertensive effect of ASX-O may be due to a NO-related mechanism. ASX-O also showed significant neuroprotective effects in ischemic mice, presumably due to its antioxidant potential. Pretreatment of the mice with ASX-O significantly shortened the latency of escaping onto the platform in the Morris water maze learning performance test. In conclusion, these results indicate that astaxanthin can exert beneficial effects in protection against hypertension and stroke and in improving memory in vascular dementia.

Neuroprotective

Food Chem Toxicol. 2010 Jun;48(6):1741-5. Epub 2010 Apr 9.

Astaxanthin improves the proliferative capacity as well as the osteogenic and adipogenic differentiation potential in neural stem cells.

Kim JH, Nam SW, Kim BW, Kim WJ, Choi YH.

Department of Biomaterial Control, Dong-Eui University, Busan, South Korea.

Abstract

In the present study, the effect of astaxanthin on improvement of the proliferative capacity as well as the osteogenic and adipogenic differentiation potential in neural stem cells (NSCs) was evaluated. Treatment of astaxanthin-induced actives cell growth in a dose-dependent and time-dependent manner. Results from a clonogenic assay clearly indicated that astaxanthin can actively stimulate proliferation of NSCs. Astaxanthin-induced improvement in the proliferative capacity of NSCs resulted in overexpression of several proliferation-related proteins. Astaxanthin-induced activation of PI3K and its downstream mediators, p-MEK, p-ERK, and p-Stat3 in NSCs resulted in subsequent induction of expression of proliferation-related transcription factors (Rex1, CDK1, and CDK2) and stemness genes (OCT4, SOX2, Nanog, and KLF4). Astaxanthin also improved the osteogenic and adipogenic differentiation potential of NSCs. Astaxanthin-treated NSCs showed prominent calcium deposits and fat formation. These results were consistent with overexpression of osteogenesis-related genes (osteonectin, RXR, and osteopontin) and adipogenesis-related genes (AP and PPAR-gamma) after astaxanthin treatment. These findings clearly demonstrated that astaxanthin acts synergistically on the regulatory circuitry that controls proliferation and differentiation of NSCs.

PMID: 20385192 [PubMed - in process]

Neuroprotective

Brain Res. 2010 Sep 7. [Epub ahead of print]

Astaxanthin upregulates heme oxygenase-1 expression through ERK1/2 pathway and its protective effect against beta-amyloid-induced cytotoxicity in SH-SY5Y cells.

Wang HQ, Sun XB, Xu YX, Zhao H, Zhu QY, Zhu CQ.

Abstract

Astaxanthin (ATX), the most abundant flavonoids in propolis, has been proven to exert neuroprotective property against glutamate-induced neurotoxicity and ischemia-reperfusion-induced apoptosis. Previous study have revealed that ATX can rescue PC12 cells from Aβ(25-35)-induced apoptotic death. However, the mechanisms by which ATX mediates its therapeutic effects in vitro are unclear. In the present study, we explored the underlying mechanisms involved in the protective effects of ATX on the Aβ(25-35)-induced cytotoxicity in SH-SY5Y cells. Pre-treatment with ATX for 4h significantly reduced the Aβ(25-35)-induced viability loss, apoptotic rate and attenuated Aβ-mediated ROS production. In addition, ATX inhibited Aβ(25-35)-induced lowered membrane potential, decreased Bcl-2/Bax ratio. We also demonstrated that ATX could prevent the activation of p38MAPK kinase pathways induced by Aβ. Moreover, we for the first time have revealed the ATX increased antioxidant enzyme heme oxygenase-1 (HO-1) expression in concentration-dependent and time-dependent manners, which were correlated with its protective effect against Aβ(25-35)-induced injury. Because the inhibitor of HO-1 activity, ZnPP reversed the protective effect of ATX against Aβ(25-35)-induced cell death. We also demonstrated that the specific ERK inhibitor, PD98059, concentration-dependently blocked on ATX-induced HO-1 expression, and meanwhile PD98059 reversed the protective effect of ATX against Aβ25-35-induced cell death. Taken together, these findings suggest that astaxanthin can induce HO-1 expression through activation of ERK signal pathways, thereby protecting the SH-SY5Y cells from Aβ(25-35)-induced oxidative cell death.

PMID: 20828541 [PubMed - as supplied by publisher]

Neuroprotective

J Clin Biochem Nutr. 2009 May;44(3):280-4. Epub 2009 Apr 25.

Preliminary Clinical Evaluation of Toxicity and Efficacy of A New Astaxanthin-rich Haematococcus pluvialis Extract.

Satoh A, Tsuji S, Okada Y, Murakami N, Urami M, Nakagawa K, Ishikura M, Katagiri M, Koga Y, Shirasawa T.

Abstract

Astaxanthin (Ax), a carotenoid ubiquitously distributed in microorganisms, fish, and crustaceans, has been known to be a potent antioxidant and hence exhibit various physiological effects. We attempted in these studies to evaluate clinical toxicity and efficacy of long-term administration of a new Ax product, by measuring biochemical and hematological blood parameters and by analyzing brain function (using CogHealth and P300 measures). Ax-rich Haematococcus pluvialis extracts equivalent to 4, 8, 20 mg of Ax dialcohol were administered to 73, 38, and 16 healthy adult volunteers, respectively, once daily for 4 weeks to evaluate safety. Ten subjects with age-related forgetfulness received an extract equivalent to 12 mg in a daily dosing regimen for 12 weeks to evaluate efficacy. As a result, no abnormality was observed and efficacy for age-related decline in cognitive and psychomotor functions was suggested.

PMID: 19430618 [PubMed - in process]PMCID: PMC2675019Free PMC Article

Neuroprotective

J Food Sci. 2009 Sep;74(7):H225-31.

Antioxidative and anti-inflammatory neuroprotective effects of astaxanthin and canthaxanthin in nerve growth factor differentiated PC12 cells.

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Abstract

Nerve growth factor differentiated PC12 cells were used to examine the antioxidative and anti-inflammatory effects of astaxanthin (AX) and canthaxanthin (CX). PC12 cells were pretreated with AX or CX at 10 or 20 muM, and followed by exposure of hydrogen peroxide (H(2)O(2)) or 1-methyl-4-phenylpyridinium ion (MPP(+)) to induce cell injury. H(2)O(2) or MPP(+) treatment significantly decreased cell viability, increased lactate dehydrogenase (LDH) release, enhanced DNA fragmentation, and lowered mitochondrial membrane potential (MMP) ($P < 0.05$). The pretreatments from AX or CX concentration-dependently alleviated H(2)O(2) or MPP(+)-induced cell death, LDH release, DNA fragmentation, and MMP reduction ($P < 0.05$). Either H(2)O(2) or MPP(+) treatment significantly increased malonyldialdehyde (MDA) and reactive oxygen species (ROS) formations, decreased glutathione content, and lowered glutathione peroxidase (GPX) and catalase activities ($P < 0.05$). The pretreatments from AX or CX significantly retained GPX and catalase activities, and decreased MDA and ROS formations ($P < 0.05$). H(2)O(2) or MPP(+) treatment significantly decreased Na(+)-K(+)-ATPase activity, elevated caspase-3 activity and levels of interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF)-alpha ($P < 0.05$); and the pretreatments from these agents significantly restored Na(+)-K(+)-ATPase activity, suppressed caspase-3 activity and release of IL-1, IL-6, and TNF-alpha ($P < 0.05$). Based on the observed antioxidative and anti-inflammatory protection from AX and CX, these 2 compounds were potent agents against neurodegenerative disorder.

PMID: 19895474 [PubMed - indexed for MEDLINE]

Neuroprotective

J Clin Biochem Nutr. 2010 Sep;47(2):121-9. Epub 2010 Jul 6.

Neuroprotective Effects of Astaxanthin in Oxygen-Glucose Deprivation in SH-SY5Y Cells and Global Cerebral Ischemia in Rat.

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Abstract

Astaxanthin (ATX), a naturally occurring carotenoid pigment, is a powerful biological antioxidant. In the present study, we investigated whether ATX pharmacologically offers neuroprotection against oxidative stress by cerebral ischemia. We found that the neuroprotective efficacy of ATX at the dose of 30 mg/kg (n = 8) was 59.5% compared with the control group (n = 3). In order to make clear the mechanism of ATX neuroprotection, the up-regulation inducible nitric oxide synthase (iNOS) and heat shock proteins (HSPs) together with the oxygen glucose deprivation (OGD) in SH-SY5Y cells were also investigated. The induction of various factors involved in oxidative stress processes such as iNOS was suppressed by the treatment of ATX at 25 and 50 μM after OGD-induced oxidative stress. In addition, Western blots showed that ATX elevated of heme oxygenase-1 (HO-1; Hsp32) and Hsp70 protein levels in in vitro. These results suggest that the neuroprotective effects of ATX were related to anti-oxidant activities in global ischemia.

PMID: 20838567 [PubMed - in process]PMCID: PMC2935152

Neuroprotective

J Med Food. 2010 Jun;13(3):548-56.

Astaxanthine secured apoptotic death of PC12 cells induced by beta-amyloid peptide 25-35: its molecular action targets.

Chang CH, Chen CY, Chiou JY, Peng RY, Peng CH.

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Abstract

Astaxanthine (ASTx) is a novel carotenoid nutraceutical occurring in many crustaceans and red yeasts. It has potent antioxidant, photoprotective, hepatodetoxicant, and anti-inflammatory activities. Documented effect of ASTx on treatment of neurodegenerative disease is still lacking. We used the beta-amyloid peptide (Abeta) 25-35-treated PC12 model to investigate the neuron-protective effect of ASTx. The parameters examined included cell viability, caspase activation, and various apoptotic biomarkers that play their critical roles in the transduction pathways independently or synergistically. Results indicated that Abeta25-35 at 30 microM suppressed cell viability by 55%, whereas ASTx was totally nontoxic below a dose of 5.00 microM. ASTx at 0.1 microM protected PC12 cells from damaging effects of Abeta25-35 in several ways: (1) by securing the cell viability; (2) by partially down-regulating the activation of caspase 3; (3) by inhibiting the expression of Bax; (4) by completely eliminating the elevation of interleukin-1beta and tumor necrosis factor-alpha; (5) by inhibiting the nuclear translocation of nuclear factor kappaB; (6) by completely suppressing the phosphorylation of p38 mitogen-activated protein kinase; (7) by completely abolishing the calcium ion influx to effectively maintain calcium homeostasis; and (8) by suppressing the majority (about 75%) of reactive oxygen species production. Conclusively, ASTx may have merit to be used as a very potential neuron protectant and an anti-early-stage Alzheimer's disease adjuvant therapy.

PMID: 20521980 [PubMed - indexed for MEDLINE]

Neuroprotective

Brain Res. 2010 Sep 21. [Epub ahead of print]

Neuroprotective effect of astaxanthin on H(2)O(2)-induced neurotoxicity in vitro and on focal cerebral ischemia in vivo.

Lu YP, Liu SY, Sun H, Wu XM, Li JJ, Zhu L.

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Abstract

Astaxanthin (AST) is a powerful antioxidant that occurs naturally in a wide variety of living organisms. Much experimental evidence has proved that AST has the function of eliminating oxygen free radicals and can protect organisms from oxidative damage. The present study was carried out to further investigate the neuroprotective effect of AST on oxidative stress induced toxicity in primary culture of cortical neurons and on focal cerebral ischemia-reperfusion induced brain damage in rats. AST, over a concentration range of 250-1000nM, attenuated 50μM H(2)O(2)-induced cell viability loss. 500nM AST pretreatment significantly inhibited H(2)O(2)-induced apoptosis measured by Hoechst 33342 staining and restored the mitochondrial membrane potential (MMP) measured by a fluorescent dye, Rhodamine 123. In vivo, AST prevented cerebral ischemic injury induced by 2h middle cerebral artery occlusion (MCAO) and 24h reperfusion in rats. Pretreatment of AST intragastrically twice at 5h and 1h prior to ischemia dramatically diminished infarct volume and improved neurological deficit in a dose-dependent manner. Nissl staining showed that the neuronal injury was significantly improved by pretreatment of AST at 80mg/kg. Taken together, these results suggest that pretreatment with AST exhibits noticeable neuroprotection against brain damage induced by ischemia-reperfusion and the antioxidant activity of AST maybe partly responsible for it.

PMID: 20846510 [PubMed - as supplied by publisher]

Neuroprotective

Cardioprotective

Atherosclerosis. 2010 Apr;209(2):520-3. Epub 2009 Oct 14.

Administration of natural astaxanthin increases serum HDL-cholesterol and adiponectin in subjects with mild hyperlipidemia.

Yoshida H, Yanai H, Ito K, Tomono Y, Koikeda T, Tsukahara H, Tada N.

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Abstract

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

PMID: 19892350 [PubMed - indexed for MEDLINE]

Cardioprotective

Am J Cardiol. 2008 May 22;101(10A):58D-68D.

Astaxanthin: a novel potential treatment for oxidative stress and inflammation in cardiovascular disease.

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Oxidative stress and inflammation are implicated in several different manifestations of cardiovascular disease (CVD). They are generated, in part, from the overproduction of reactive oxygen species (ROS) and reactive nitrogen species (RNS) that activate transcriptional messengers, such as nuclear factor-kappaB, tangibly contributing to endothelial dysfunction, the initiation and progression of atherosclerosis, irreversible damage after ischemic reperfusion, and even arrhythmia, such as atrial fibrillation. Despite this connection between oxidative stress and CVD, there are currently no recognized therapeutic interventions to address this important unmet need. Antioxidants that provide a broad, "upstream" approach via ROS/RNS quenching or free radical chain breaking seem an appropriate therapeutic option based on epidemiologic, dietary, and in vivo animal model data. However, human clinical trials with several different well-known agents, such as vitamin E and beta-carotene, have been disappointing. Does this mean antioxidants as a class are ineffective, or rather that the "right" compound(s) have yet to be found, their mechanisms of action understood, and their appropriate targeting and dosages determined? A large class of potent naturally-occurring antioxidants exploited by nature-the oxygenated carotenoids (xanthophylls)-have demonstrated utility in their natural form but have eluded development as successful targeted therapeutic agents up to the present time. This article characterizes the mechanism by which this novel group of antioxidants function and reviews their preclinical development. Results from multiple species support the antioxidant/anti-inflammatory properties of the prototype compound, astaxanthin, establishing it as an appropriate candidate for development as a therapeutic agent for cardiovascular oxidative stress and inflammation.

Publication Types:

- Review

PMID: 18474276 [PubMed - indexed for MEDLINE]

Cardioprotective

Am J Cardiol. 2008 May 22;101(10A):20D-29D.

Biologic activity of carotenoids related to distinct membrane physicochemical interactions.

McNulty H, **Jacob RF**, **Mason RP**.

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Carotenoids are naturally occurring organic pigments that are believed to have therapeutic benefit in treating cardiovascular disease (CVD) because of their antioxidant properties. However, prospective randomized trials have failed to demonstrate a consistent benefit for the carotenoid beta-carotene in patients at risk for CVD. The basis for this apparent paradox is not well understood but may be attributed to the distinct antioxidant properties of various carotenoids resulting from their structure-dependent physicochemical interactions with biologic membranes. To test this hypothesis, we measured the effects of astaxanthin, zeaxanthin, lutein, beta-carotene, and lycopene on lipid peroxidation using model membranes enriched with polyunsaturated fatty acids. The correlative effects of these compounds on membrane structure were determined using small-angle x-ray diffraction approaches. The nonpolar carotenoids, lycopene and beta-carotene, disordered the membrane bilayer and stimulated membrane lipid peroxidation (>85% increase in lipid hydroperoxide levels), whereas astaxanthin (a polar carotenoid) preserved membrane structure and exhibited significant antioxidant activity (>40% decrease in lipid hydroperoxide levels). These results suggest that the antioxidant potential of carotenoids is dependent on their distinct membrane lipid interactions. This relation of structure and function may explain the differences in biologic activity reported for various carotenoids, with important therapeutic implications.

Publication Types:

PMID: 18474269 [PubMed - indexed for MEDLINE]

Cardioprotective

Mol Cell Biochem. 2008 Feb;309(1-2):61-8. Epub 2007 Nov 16.

The protective role of carotenoids against 7-keto-cholesterol formation in solution.

Palozza P, **Barone E**, **Mancuso C**, **Picci N**.

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The antioxidant activity of beta-carotene and oxygenated carotenoids lutein, canthaxanthin, and astaxanthin was investigated during spontaneous and peroxyl-radical-induced cholesterol oxidation. Cholesterol oxidation, measured as generation of 7-keto-cholesterol (7-KC), was evaluated in a heterogeneous solution with cholesterol, AAPH, and carotenoids solubilized in tetrahydrofuran and in water, and in a homogeneous solution of chlorobenzene, with AIBN as a prooxidant. The formation of 7-KC was dependent on temperature and on cholesterol and prooxidant concentrations. All the carotenoids tested, exhibited significant antioxidant activity by inhibiting spontaneous, AAPH- and AIBN-induced formation of 7-KC, although the overall order of efficacy of these compounds was astaxanthin > canthaxanthin > lutein = beta-carotene. The finding that carotenoids exert protective effects on spontaneous and free radical-induced cholesterol oxidation may have important beneficial effects on human health, by limiting the formation of atheroma and by inhibiting cholesterol oxidation in food processing or storage.

Publication Types:

PMID: 18008144 [PubMed - indexed for MEDLINE]

Cardioprotective

Int J Vitam Nutr Res. 2007 Jan;77(1):3-11.

Effects of astaxanthin supplementation on lipid peroxidation.

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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.

Publication Types:

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Cardioprotective

BMC Nephrol. 2008 Dec 18;9:17.

Astaxanthin vs placebo on arterial stiffness, oxidative stress and inflammation in renal transplant patients (Xanthin): a randomised controlled trial.

Fassett RG, **Healy H**, **Driver R**, **Robertson IK**, **Geraghty DP**, **Sharman JE**, **Coombes JS**.
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BACKGROUND: There is evidence that renal transplant recipients have accelerated atherosclerosis manifest by increased cardiovascular morbidity and mortality. The high incidence of atherosclerosis is, in part, related to increased arterial stiffness, vascular dysfunction, elevated oxidative stress and inflammation associated with immunosuppressive therapy. The dietary supplement astaxanthin has shown promise as an antioxidant and anti-inflammatory therapeutic agent in cardiovascular disease. The aim of this trial is to investigate the effects of astaxanthin supplementation on arterial stiffness, oxidative stress and inflammation in renal transplant patients. METHOD AND DESIGN: This is a randomised, placebo controlled clinical trial. A total of 66 renal transplant recipients will be enrolled and allocated to receive either 12 mg/day of astaxanthin or an identical placebo for one-year. Patients will be stratified into four groups according to the type of immunosuppressant therapy they receive: 1) cyclosporine, 2) sirolimus, 3) tacrolimus or 4) prednisolone+/-azathioprine, mycophenolate mofetil or mycophenolate sodium. Primary outcome measures will be changes in 1) arterial stiffness measured by aortic pulse wave velocity (PWV), 2) oxidative stress assessed by plasma isoprostanes and 3) inflammation by plasma pentraxin 3. Secondary outcomes will include changes in vascular function assessed using the brachial artery reactivity (BAR) technique, carotid artery intimal medial thickness (CIMT), augmentation index (AIx), left ventricular afterload and additional measures of oxidative stress and inflammation. Patients will undergo these measures at baseline, six and 12 months. DISCUSSION: The results of this study will help determine the efficacy of astaxanthin on vascular structure, oxidative stress and inflammation in renal transplant patients. This may lead to a larger intervention trial assessing cardiovascular morbidity and mortality. TRIAL REGISTRATION: ACTRN12608000159358.

PMID: 19091127 [PubMed - indexed for MEDLINE]

PMCID: PMC2666668

Cardioprotective

J Clin Biochem Nutr. 2008 Sep;43(2):69-74.

Effects of astaxanthin on human blood rheology.

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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.

PMID: 18818755 [PubMed - in process]

PMCID: PMC2533721

Cardioprotective

Pharmacology. 2008;82(1):67-73. Epub 2008 May 14.

Disodium disuccinate astaxanthin prevents carotid artery rethrombosis and ex vivo platelet activation.

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BACKGROUND/AIMS:The disodium disuccinate derivative of astaxanthin (DDA) is a carotenoid antioxidant under development for the treatment of ischemic cardiovascular events. Recent evidence suggests that reactive oxygen species (ROS) play an important role in platelet activation. This study seeks to investigate the effects of a reactive oxygen species quencher, DDA, in a canine model of carotid artery thrombosis. METHODS: After formation of an occlusive carotid thrombus, dogs were administered recombinant tissue plasminogen activator intra-arterially to achieve thrombolysis in the presence of either 0.9% NaCl solution or DDA (10-50 mg/kg i.v. infusion). Ex vivo platelet aggregation and tongue bleeding times were measured before and after drug administration. Residual thrombus mass was analyzed at the end of each experiment. RESULTS:The data indicated a dose- dependent reduction in the incidence of carotid artery rethrombosis. In addition, platelet aggregation and thrombus weights were dose-dependently inhibited by DDA. No change was recorded in tongue bleeding time among the treatment groups. CONCLUSIONS:The data demonstrate that at the doses used in this study, DDA significantly reduced the incidence of secondary thrombosis while maintaining normal hemostasis. The results suggest that upon further study, DDA may one day find utility in revascularization procedures.

PMID: 18477858 [PubMed - indexed for MEDLINE]

Cardioprotective

Arzneimittelforschung. 2007;57(1):26-30.

Eulipidemic effects of berberine administered alone or in combination with other natural cholesterol-lowering agents. A single-blind clinical investigation.

Cicero AF, **Rovati LC**, **Setnikar I**.

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Berberine (BERB) and a combination (COMB) of berberine (CAS 2086-83-1) with policosanol (CAS 557-61-9), red yeast extract (containing monacolin, CAS 557-61-9), folic acid and astaxanthin were orally administered daily for 4 weeks to 40 subjects with moderate dyslipidemias divided in two parallel groups each of 20 subjects. Total cholesterol (TC), LDL, HDL, Non HDL, ApoB, ApoA, Lp(a) and triglycerides (TG) were measured before and at the end of treatments. BERB and COMB significantly reduced TC (respectively by 16% and 20%), LDL (by 20% and 25%), ApoB (by 15% and 29%) and TG (by 22% and 26%), and increased HDL (by 6.6% and 5.1%). Adverse events or impairments of liver transaminases or of CPK were not observed. In conclusion, food supplements containing natural products such as berberine, policosanol, red yeast extracts, folic acid and astaxanthin could be a useful support to diet and life style changes to correct dyslipidemias and to reduce cardiovascular risk in subjects with moderate mixed dyslipidemias.

Publication Types:

PMID: 17341006 [PubMed - indexed for MEDLINE]

Cardioprotective

Cardiovasc Hematol Agents Med Chem. 2006 Oct;4(4):335-49.

Retrometabolic syntheses of astaxanthin (3,3'-dihydroxy-beta,beta-carotene-4,4'-dione) conjugates: a novel approach to oral and parenteral cardio-protection.

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Disodium disuccinate astaxanthin has potent cardioprotective effects in animals, with demonstrated preclinical efficacy in the rat, rabbit, and canine models of experimental infarction. It has been effective in subchronic and acute dosing regimens after parenteral administration, and recently published data in rats demonstrate that oral cardioprotection is also readily achieved. Myocardial salvage in the canine can reach 100% with a 4-day subchronic dosing regimen; single-dose I.V. cardioprotection, when given 2 hours before experimental coronary occlusion, is on average two-thirds of that achieved with the subchronic regimen in dogs. In conscious animals, no effects on hemodynamic parameters have been observed. Recently, the beneficial properties of this prototypical astaxanthin conjugate have been extended to include second- and third-generation compounds with improved pharmacokinetic and/or potency profiles. The primary mechanism of cardioprotection appears to be antioxidant activity: potent direct scavenging of the lynchpin radical in ischemia-reperfusion injury, superoxide anion, has been documented in appropriate model systems. In addition, modulation of serum complement activity, reduction of the levels of deposition of C-reactive protein (CRP) and the membrane attack complex (MAC) in infarcted tissue, and reduction in oxidative stress markers from the arachidonic acid and linoleic acid pathways also suggest a significant anti-inflammatory component to the mechanism of cardioprotection. Favorable plasma protein binding has been demonstrated in vitro for several astaxanthin conjugates; this binding capacity overcomes the supramolecular assembly of the compounds that occurs in aqueous solution, which in itself improves the stability and shelf-life of aqueous formulations. Astaxanthin readily populates cardiac tissue after metabolic hydrolysis of both oral and parenteral administration of the astaxanthin ester derivates, providing a reservoir of cardioprotective agent with a significant half-life due to favorable ADME in mammals. Due to the well-documented safety profile of astaxanthin in humans, disodium disuccinate astaxanthin may well find clinical utility in cardiovascular applications in humans following successful completion of preclinical and clinical pharmacology and toxicology studies in animals and humans, respectively.

Publication Types:

PMID: 17073610 [PubMed - indexed for MEDLINE]

Cardioprotective

J Cardiovasc Pharmacol. 2006;47 Suppl 1:S7-14.

Rofecoxib increases susceptibility of human LDL and membrane lipids to oxidative damage: a mechanism of cardiotoxicity.

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Clinical investigations have demonstrated a relationship between the extended use of rofecoxib and the increased risk for atherothrombotic events. This has led to the removal of rofecoxib from the market and concern over the cardiovascular safety of other cyclooxygenase (COX)-2 selective agents. Experimental findings from independent laboratories now indicate that the cardiotoxicity of rofecoxib may not be a class effect but because of its intrinsic chemical properties. Specifically, rofecoxib has been shown to increase the susceptibility of human low-density lipoprotein and cellular membrane lipids to oxidative modification, a contributing factor to plaque instability and thrombus formation. Independently of COX-2 inhibition, rofecoxib also promoted the nonenzymatic formation of isoprostanes and reactive aldehydes from biologic lipids. The basis for these observations is that rofecoxib alters lipid structure and readily forms a reactive maleic anhydride in the presence of oxygen. By contrast, other selective (celecoxib, valdecoxib) and nonselective (naproxen, diclofenac) inhibitors did not influence rates of low-density lipoprotein and membrane lipid oxidation. We have now further confirmed these findings by demonstrating that the prooxidant activity of rofecoxib can be blocked by the potent antioxidant astaxanthin in homochiral form (all-trans 3S, 3'S). These findings provide a mechanistic rationale for differences in cardiovascular risk among COX-selective inhibitors because of their intrinsic physicochemical properties.

PMID: 16785833 [PubMed - indexed for MEDLINE]

Cardioprotective

Biol Pharm Bull. 2006 Apr;29(4):684-8.

Antihypertensive potential and mechanism of action of astaxanthin: III. Antioxidant and histopathological effects in spontaneously hypertensive rats.

Hussein G, **Goto H**, **Oda S**, **Sankawa U**, **Matsumoto K**, **Watanabe H**.

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We investigated the effects of a dietary astaxanthin (ASX-O) on oxidative parameters in spontaneously hypertensive rats (SHR), by determination of the level of nitric oxide (NO) end products nitrite/nitrate (NO2-/NO3-) and lipid peroxidation in ASX-O-treated SHR. Oral administration of the ASX-O significantly reduced the plasma level of NO2-/NO3- compared to the control vehicle ($p<0.05$). The lipid peroxidation level, however, was reduced in both ASX-O- and olive oil-treated groups. We also analyzed the post-treatment effects of ASX-O on the vascular tissues by examining the changes in the aorta and coronary arteries and arterioles. The dietary ASX-O showed significant reduction in the elastin bands in the rat aorta ($p<0.05$). It also significantly decreased the [wall : lumen] aerial ratio of the coronary arteries. These results suggest that ASX-O can modulate the oxidative condition and may improve vascular elastin and arterial wall thickness in hypertension.

Publication Types:

PMID: 16595899 [PubMed - indexed for MEDLINE]

Cardioprotective

J Nat Prod. 2006 Mar;69(3):443-9.

Astaxanthin, a carotenoid with potential in human health and nutrition.

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Astaxanthin (1), a red-orange carotenoid pigment, is a powerful biological antioxidant that occurs naturally in a wide variety of living organisms. The potent antioxidant property of 1 has been implicated in its various biological activities demonstrated in both experimental animals and clinical studies. Compound 1 has considerable potential and promising applications in human health and nutrition. In this review, the recent scientific literature (from 2002 to 2005) is covered on the most significant activities of 1, including its antioxidative and anti-inflammatory properties, its effects on cancer, diabetes, the immune system, and ocular health, and other related aspects. We also discuss the green microalga Haematococcus pluvialis, the richest source of natural 1, and its utilization in the promotion of human health, including the antihypertensive and neuroprotective potentials of 1, emphasizing our experimental data on the effects of dietary astaxanthin on blood pressure, stroke, and vascular dementia in animal models, is described.

Publication Types:

PMID: 16562856 [PubMed - indexed for MEDLINE]

Cardioprotective

Life Sci. 2006 Jun 6;79(2):162-74. Epub 2006 Feb 8.

The effects of oral Cardax (disodium disuccinate astaxanthin) on multiple independent oxidative stress markers in a mouse peritoneal inflammation model: influence on 5-lipoxygenase in vitro and in vivo.

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Disodium disuccinate astaxanthin ('rac'-dAST; Cardax) is a water-dispersible C40 carotenoid derivative under development for oral and parenteral administration for cardioprotection of the at-risk ischemic cardiovascular patient. In experimental infarction models in animals (rats, rabbits, and dogs), significant myocardial salvage has been obtained, up to 100% at the appropriate dose in dogs. The documented mechanism of action in vitro includes direct scavenging of biologically produced superoxide anion; in vivo in rabbits, modulation of the complement activity of serum has also been shown. A direct correlation between administration of the test compound in animals and reductions of multiple, independent markers of oxidative stress in serum was recently obtained in a rat experimental infarction model. For the current study, it was hypothesized that oral Cardax administration would inhibit oxidative damage of multiple relevant biological targets in a representative, well-characterized murine peritoneal inflammation model. A previously developed mass spectrometry-based (LC/ESI/MS/MS) approach was used to interrogate multiple distinct pathways of oxidation in a black mouse (C57/BL6) model system. In vivo markers of oxidant stress from peritoneal lavage samples (supernatants) were evaluated in mice on day eight (8) after treatment with either Cardax or vehicle (lipophilic emulsion without drug) orally by gavage at 500 mg/kg once per day for seven (7) days at five (5) time points: (1) baseline prior to treatment (t=0); (2) 16 h following intraperitoneal (i.p.) injection with thioglycollate to elicit a neutrophilic infiltrate; (3) 4 h following i.p. injection of yeast cell wall (zymosan; t=16 h/4 h thioglycollate+zymosan); (4) 72 h following i.p. injection with thioglycollate to elicit monocyte/macrophage infiltration; and (5) 72 h/4 h thioglycollate+zymosan. A statistically significant sparing effect on the arachidonic acid (AA) and linoleic acid (LA) substrates was observed at time points two and five. When normalized to the concentration of the oxidative substrates, statistically significant reductions of 8-isoprostane-F(2alpha) (8-iso-F(2alpha)) at time point three (maximal neutrophil recruitment/activation), and 5-HETE, 5-oxo-EET, 11-HETE, 9-HODE, and PGF(2alpha) at time point five (maximal monocyte/macrophage recruitment/activation) were observed. Subsequently, the direct interaction of the optically inactive stereoisomer of Cardax (meso-dAST) with human 5-lipoxygenase (5-LOX) was evaluated in vitro with circular dichroism (CD) and electronic absorption (UV/Vis) spectroscopy, and subsequent molecular docking calculations were made using mammalian 15-LOX as a surrogate (for which XRC data has been reported). The results suggested that the meso-compound was capable of interaction with, and binding to, the solvent-exposed surface of the enzyme. These preliminary studies provide the foundation for more detailed evaluation of the therapeutic effects of this compound on the 5-LOX enzyme, important in chronic diseases such as atherosclerosis, asthma, and prostate cancer in humans.

PMID: 16466747 [PubMed - indexed for MEDLINE]

Cardioprotective

Mol Cell Biochem. 2006 Feb;283(1-2):23-30.

Seven day oral supplementation with Cardax (disodium disuccinate astaxanthin) provides significant cardioprotection and reduces oxidative stress in rats.

Gross GJ, **Hazen SL**, **Lockwood SF**.

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In the current study, the improved oral bioavailability of a synthetic astaxanthin derivative (Cardax; disodium disuccinate astaxanthin) was utilized to evaluate its potential effects as a cardioprotective agent after 7-day subchronic oral administration as a feed supplement to Sprague-Dawley rats. Animals received one of two concentrations of Cardax in feed (0.1 and 0.4%; approximately 125 and 500 mg/kg/day, respectively) or control feed without drug for 7 days prior to the infarct study carried out on day 8. Thirty minutes of occlusion of the left anterior descending (LAD) coronary artery was followed by 2 h of reperfusion prior to sacrifice, a regimen which resulted in a mean infarct size (IS) as a percentage (%) of the area at risk (AAR; IS/AAR,%) of 61 +/- 1.8%. The AAR was quantified by Patent blue dye injection, and IS was determined by triphenyltetrazolium chloride (TTC) staining. Cardax at 0.1 and 0.4% in feed for 7 days resulted in a significant mean reduction in IS/AAR,% to 45 +/- 2.0% (26% salvage) and 39 +/- 1.5% (36% salvage), respectively. Myocardial levels of free astaxanthin achieved after 7-day supplementation at each of the two concentrations (400 +/- 65 nM and 1634 +/- 90 nM, respectively) demonstrated excellent solid-tissue target organ loading after oral supplementation. Parallel trends in reduction of plasma levels of multiple lipid peroxidation products with disodium disuccinate astaxanthin supplementation were observed, consistent with the documented in vitro antioxidant mechanism of action. These results extend the potential utility of this compound for cardioprotection to the elective human cardiovascular patient population, for which 7-day oral pre-treatment (as with statins) provides significant reductions in induced periprocedural infarct size.

PMID: 16444582 [PubMed - indexed for MEDLINE]

Cardioprotective

Cardiovasc Drug Rev. 2005 Fall;23(3):199-216.

Disodium disuccinate astaxanthin (Cardax): antioxidant and antiinflammatory cardioprotection.

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Disodium disuccinate astaxanthin (Cardax), DDA) has cardioprotective effects in the rat, rabbit, and canine models of experimental infarction. It is highly effective by parenteral administration in subchronic and acute dosing regimens. Unpublished data in rats suggest that oral cardioprotection is also readily achievable. DDA-induced myocardial salvage in the canine can reach 100% with a 4-day subchronic dosing regimen. At a single i.v. dose DDA is cardioprotective, when given 2 h before experimental coronary occlusion, but the protection is on the average two-thirds of that achieved with the subchronic regimen in dogs. In conscious animals DDA has no effects on hemodynamic parameters. The primary mechanism of cardioprotection appears to be antioxidant activity involving direct scavenging of superoxide anion, the lynchpin radical in ischemia-reperfusion injury. In addition, modulation of serum complement activity, as well as the reduction in the levels of C-reactive protein (CRP) and the membrane attack complex (MAC) in infarcted tissue suggest a significant antiinflammatory component in the mechanism of cardioprotective action of DDA. Stoichiometric binding of the meso-form of the compound to human serum albumin (HSA) has been demonstrated in vitro. This binding capacity overcomes the supramolecular assembly of the compound in aqueous solution, which by itself improves the stability and shelf life of aqueous formulations. Non-esterified astaxanthin readily enters cardiac tissue after either oral or parenteral administration, providing a reservoir of a cardioprotective agent with a significant half-life due to favorable ADME in mammals. Due to the well-documented safety profile of non-esterified astaxanthin in humans, disodium disuccinate astaxanthin may well find clinical utility in cardiovascular indications in humans following successful completion of preclinical and clinical pharmacology and toxicology studies.

Publication Types:

PMID: 16252014 [PubMed - indexed for MEDLINE]

Cardioprotective

Arzneimittelforschung. 2005;55(6):312-7.

Antiatherosclerotic efficacy of policosanol, red yeast rice extract and astaxanthin in the rabbit.

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The effects of policosanol (P), of extract of red yeast rice (rice fermented with Monascus purpureus) (RYE) and of astaxanthin (A) (constituents of Armolipid) were investigated in a model of experimental atherosclerosis provoked in the rabbit by atherogenic cholesterol-enriched feed (ACEF). P and RYE and their combination were able to lower the increase of serum total cholesterol and of LDL cholesterol elicited by 3-month feeding with ACEF. They also were able to reduce the increase of blood malondialdehyde (MDA), a tracer of lipid peroxidation by the free radicals released by ACEF. When combined, the substances developed either additive or potentiated effects, supporting the rationale of their combination. Remarkable was the protective effect on lipid infiltration in the aortic wall provoked by ACEF, which was reduced by P and by RYE and almost completely prevented by the addition of A to the P-RYE combination. The results support the rationale of a combination of P, RYE and A as a useful food supplement in hyperlipemic patients.

PMID: 16032970 [PubMed - indexed for MEDLINE]

Cardioprotective

Mol Cell Biochem. 2005 Apr;272(1-2):221-7.

Acute and chronic administration of disodium disuccinate astaxanthin (Cardax) produces marked cardioprotection in dog hearts.

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Previous results from our laboratory have shown that a novel carotenoid derivative (disodium disuccinate astaxanthin; Cardax) produced dose-related reductions in myocardial infarct size (IS) in Sprague-Dawley rats when it was administered at any of three doses (25, 50 and 75 mg/kg, iv) on four consecutive days, followed by the acute infarct size study on day 5. Maximum salvage occurred at the highest dose (75 mg/kg) tested, and was shown as a 56% reduction in IS. In the present follow-up study, we used a more relevant large animal model, the dog, and looked at the effect of administering Cardax iv either acutely 2 h prior to occlusion (N = 8) or for 4 days at 50 mg/kg iv as previously done in the rat model (N = 6). The results were compared to a saline vehicle-treated group (N = 10). In all groups, dogs were subjected to 60 min of left anterior descending (LAD) coronary artery occlusion and 3 h of reperfusion. IS was determined using a triphenyltetrazolium chloride (TTZ) histochemical stain and was expressed as a percent of the area at risk (IS/AAR). IS/AAR was 20.9 +/- 1.6 % (mean +/- S.E.M.) in controls and was reduced to 11.0 +/- 1.7% (47.3% salvage; $p < 0.01$) in dogs treated only once iv at 2 h prior to occlusion, and 6.6 +/- 2.8% (68.4% salvage; $p < 0.001$) in dogs treated for 4 days. In the chronic treatment group, two of the three dogs with plasma concentrations of non-esterified astaxanthin above 1 microM had 0% IS/AAR (100% cardioprotection). These results suggest that Cardax has marked cardioprotective properties in both rodents and canines. Thus, Cardax may be a novel and powerful new means to prevent myocardial injury and/or necrosis associated with elective and/or urgent cardiac surgical interventions such as coronary angioplasty and stenting, as well as coronary artery bypass surgery (CABG).

PMID: 16010990 [PubMed - indexed for MEDLINE]

Cardioprotective

Biol Pharm Bull. 2005 Jun;28(6):967-71.

Antihypertensive potential and mechanism of action of astaxanthin: II. Vascular reactivity and hemorheology in spontaneously hypertensive rats.

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The current study was designed to determine the effects of a dietary astaxanthin (ASX-O) on vascular reactivity in spontaneously hypertensive rats (SHR), in order to verify its antihypertensive action mechanism. We evaluated contractions induced by phenylephrine (Phe), angiotensin II (Ang II) and the xanthine/xanthine oxidase (Xan/XOD) system, and relaxations induced by sodium nitroprusside (SNP) as well as endothelium-dependent relaxations mediated by acetylcholine (ACh) in thoracic aorta of the SHR, with and without ASX-O intervention. We also investigated the effects of ASX-O on blood rheology using a microchannel array system. In this study, ASX-O showed a significant modulatory effect on nitric oxide (NO)-induced vasorelaxation by the NO-donor SNP ($p<0.05$). However, it did not show significant effects in restoring the impaired endothelium-dependent relaxation to ACh in the SHR. On the other hand, the constrictive effects by Phe, Ang II and Xan/XOD were ameliorated by ASX-O ($p<0.05$). ASX-O also demonstrated significant hemorheological effect by decreasing the microchannel transit time of whole blood. In conclusion, the results suggest that ASX-O may act in modulating the blood fluidity in hypertension, and that the antihypertensive effects of ASX-O may be exerted through mechanisms including normalization of the sensitivity of the adrenoceptor sympathetic pathway, particularly [alpha]-adrenoceptors, and by restoration of the vascular tone through attenuation of the Ang II- and reactive oxygen species (ROS)-induced vasoconstriction.

Publication Types:

PMID: 15930728 [PubMed - indexed for MEDLINE]

Cardioprotective

J Pharmacol Exp Ther. 2005 Aug;314(2):686-92. Epub 2005 May 4.

Disodium Disuccinate Astaxanthin (Cardax) attenuates complement activation and reduces myocardial injury following ischemia/reperfusion.

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Carotenoids are a naturally occurring group of compounds that possess antioxidant properties. Most natural carotenoids display poor aqueous solubility and tend to form aggregates in solution. Disodium disuccinate astaxanthin (DDA; Cardax) is a water-dispersible synthetic carotenoid that rapidly and preferentially associates with serum albumin, thereby preventing the formation of supramolecular complexes and facilitating its efficacy after parenteral administration. This study investigated the ability of DDA to reduce inflammation and myocardial injury in a rabbit model of ischemia/reperfusion. DDA (50 mg/kg/day) or saline was administered i.v. for 4 consecutive days before the initiation of the protocol for induction of myocardial ischemia/reperfusion. On the 5th day, rabbits underwent 30 min of coronary artery occlusion, followed by a 3-h reperfusion period. Myocardial infarct size, as a percentage of the area at risk, was calculated for both groups. Infarct size was 52.5 +/- 7.5% in the vehicle-treated ($n = 9$) and 25.8 +/- 4.7% in the DDA-treated ($n = 9$) animals ($p < 0.01$ versus vehicle; mean myocardial salvage = 51%). To evaluate the anti-inflammatory effects of DDA, complement activity was assessed at the end of reperfusion using a red blood cell lysis assay. DDA administration significantly reduced ($p < 0.01$) the activation of the complement system in the serum. The current results, coupled with the well established antioxidant ability of carotenoids, suggest that the mechanism(s) of action by which DDA reduces the tissue damage associated with reperfusion injury may include both antioxidant and anticomplement components.

Publication Types:

PMID: 15872041 [PubMed - indexed for MEDLINE]

Cardioprotective

Biol Pharm Bull. 2005 Jan;28(1):47-52.

Antihypertensive and neuroprotective effects of astaxanthin in experimental animals.

Hussein G, **Nakamura M**, **Zhao Q**, **Iguchi T**, **Goto H**, **Sankawa U**, **Watanabe H**.

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Astaxanthin is a natural antioxidant carotenoid that occurs in a wide variety of living organisms. We investigated, for the first time, antihypertensive effects of astaxanthin (ASX-O) in spontaneously hypertensive rats (SHR). Oral administration of ASX-O for 14 d induced a significant reduction in the arterial blood pressure (BP) in SHR but not in normotensive Wistar Kyoto (WKY) strain. The long-term administration of ASX-O (50 mg/kg) for 5 weeks in stroke prone SHR (SHR-SP) induced a significant reduction in the BP. It also delayed the incidence of stroke in the SHR-SP. To investigate the action mechanism of ASX-O, the effects on PGF(2alpha)-induced contractions of rat aorta treated with NG-nitro-L-arginine methyl ester (L-NAME) were studied in vitro. ASX-O (1 to 10 microM) induced vasorelaxation mediated by nitric oxide (NO). The results suggest that the antihypertensive effect of ASX-O may be due to a NO-related mechanism. ASX-O also showed significant neuroprotective effects in ischemic mice, presumably due to its antioxidant potential. Pretreatment of the mice with ASX-O significantly shortened the latency of escaping onto the platform in the Morris water maze learning performance test. In conclusion, these results indicate that astaxanthin can exert beneficial effects in protection against hypertension and stroke and in improving memory in vascular dementia.

Publication Types:

PMID: 15635162 [PubMed - indexed for MEDLINE]

Cardioprotective

J Mol Cell Cardiol. 2004 Nov;37(5):969-78.

Alpha-tocopherol and astaxanthin decrease macrophage infiltration, apoptosis and vulnerability in atheroma of hyperlipidaemic rabbits.

Li W, **Hellsten A**, **Jacobsson LS**, **Blomqvist HM**, **Olsson AG**, **Yuan XM**.

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The composition of atherosclerotic plaques, not just macroscopical lesion size, has been implicated in their susceptibility to rupture and the risk of thrombus formation. By focusing on the quality of lipids, macrophages, apoptosis, collagen, metalloproteinase expression and plaque integrity, we evaluated the possible anti-atherosclerotic effect of the antioxidants alpha-tocopherol and astaxanthin in Watanabe heritable hyperlipidemic (WHHL) rabbits. Thirty-one WHHL rabbits were divided into three groups and were fed a standard diet, as controls (N =10), or a standard diet with the addition of 500 mg alpha-tocopherol per kg feed (N =11) or 100 mg astaxanthin per kg feed (N =10) for 24 weeks. We found that both antioxidants, particularly astaxanthin, significantly decreased macrophage infiltration in the plaques although they did not affect lipid accumulation. All lesions in the astaxanthin-treated rabbits were classified as early plaques according to the distribution of collagen and smooth muscle cells. Both antioxidants also improved plaque stability and significantly diminished apoptosis, which mainly occurred in macrophages, matrix metalloproteinase three expressions and plaque ruptures. Although neither antioxidant altered the positive correlations between the lesion size and lipid accumulation, the lesion size and apoptosis were only positively correlated in the control group. Astaxanthin and alpha-tocopherol may improve plaque stability by decreasing macrophage infiltration and apoptosis in this atherosclerotic setting. Apoptosis reduction by alpha-tocopherol and astaxanthin may be a new anti-atherogenic property of these antioxidants.

Publication Types:

PMID: 15522274 [PubMed - indexed for MEDLINE]

Cardioprotective

Life Sci. 2004 May 28;75(2):215-24.

Cardioprotection and myocardial salvage by a disodium disuccinate astaxanthin derivative (Cardax).

Gross GJ, **Lockwood SF**.

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Cardioprotection in humans by carotenoids has been inferred from observational and epidemiologic studies, however, direct studies of cardioprotection and myocardial salvage by carotenoids are lacking. In the current study, intravenous (I.V.) pre-treatment with a novel carotenoid derivative (disodium disuccinate astaxanthin; Cardax) was evaluated as a myocardial salvage agent in a Sprague-Dawley rat infarct model. Animals were dosed once per day I.V. by tail vein injection for 4 days at one of 3 doses (25, 50, and 75 mg/kg) prior to the infarct study carried out on day 5. The results were compared with control animals treated with saline vehicle. Thirty (30) minutes of occlusion of the left anterior descending (LAD) coronary artery was followed by 2 hours of reperfusion prior to sacrifice, a regimen which resulted in a mean infarct size (IS) as a percent (%) of the area at risk (AAR) of 59 +/- 3%. Area at risk was quantified by Patent blue dye injection, and infarct size (IS) was determined by triphenyltetrazolium chloride (TTC) staining. Cardax at 50 and 75 mg/kg for 4 days resulted in a significant mean reduction in IS/AAR to 35 +/- 3% (41% salvage) and 26 +/- 2% (56% salvage), respectively. Infarct size and myocardial salvage were significantly, and linearly, correlated with plasma levels of non-esterified, free astaxanthin at the end of reperfusion. These results suggest that parenteral Cardax may find utility in those clinical applications where pre-treatment of patients at risk for myocardial infarction is performed.

Publication Types:

PMID: 15120573 [PubMed - indexed for MEDLINE]

Cardioprotective

J Atheroscler Thromb. 2000;7(4):216-22.

Inhibition of low-density lipoprotein oxidation by astaxanthin.

Iwamoto T, **Hosoda K**, **Hirano R**, **Kurata H**, **Matsumoto A**, **Miki W**, **Kamiyama M**, **Itakura H**, **Yamamoto S**, **Kondo K**.

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Marine animals produce astaxanthin which is a carotenoid and antioxidant. In this study we determined the in vitro and ex vivo effects of astaxanthin on LDL oxidation. The oxidation of LDL was measured in a 1 ml reaction system consisting of increasing concentrations of astaxanthin (12.5, 25.0, 50.0 microg/ml), 400 microM V-70 (2, 2'-azobis(4-methoxy-2, 4-dimethylvaleronitrile)), and LDL (70 microg/ml protein). Astaxanthin dose, dependently significantly prolonged the oxidation lag time (31.5, 45.4, 65.0 min) compared with the control (19.9 min). For the ex vivo study 24 volunteers (mean age 28.2 [SD 7.8] years) consumed astaxanthin at doses of 1.8, 3.6,14.4 and 21.6 mg per day for 14 days. No other changes were made in the diet. Fasting venous blood samples were taken at days 0, +14. LDL lag time was longer (5.0, 26.2, 42.3 and 30.7% respectively) compared with day 0 after consuming astaxanthin at doses of 1.8, 3.6,14.4 and 21.6 mg for 14 days compared with day 0, but there was no difference in oxidation of LDL between day 0 (lag time 59.9+/-7.2 min) and day 14 (57.2+/-6.0 min) in the control group. Our results provide evidence that consumption of marine animals producing astaxanthin inhibits LDL oxidation and possibly therefore contributes to the prevention of atherosclerosis.

Publication Types:

PMID: 11521685 [PubMed - indexed for MEDLINE]

Cardioprotective

Biull Eksp Biol Med. 1997 Mar;123(3):285-8.

[Astaxanthine-induced inhibition of oxidation of apolipoprotein B-containing lipoproteins in human blood]

[Article in Russian]

Kukharchuk VV, **Shumaev KB**, **Dmitrovskiĭ AA**, **Cherniad'eva IF**, **Bykhovskiĭ VIa**.

PMID: 9162235 [PubMed - indexed for MEDLINE]

Cardioprotective

Prog Med F0664B 0287-3648 VOL.24;NO.6;PAGE.1437-1442(2004)

Multivitamin and Carotenoid Supplements

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Abstract;Vitamins are regarded as essential nutrients for health and maintain stable tissue environments. Vitamins and carotenoids have multiple roles both as participants in many important metabolic processes throughout the body and to counter the oxidative stress resulting from normal metabolism and daily exposure to environmental agents. Epidemiological studies have consistently indicated that the consumption of vegetables and fruits is inversely related to the incidence of cardiovascular and cerebrovascular diseases and cancer. Although the majority of vitamins and carotenoids are derived from these foods, foods of animal origin also contribute supplementation of these nutrients. Marine animals supply astaxanthin which is a carotenoid and antioxidant. We studied the effects of astaxanthin on in vitro and ex vivo LDL oxidation. Astaxanthin prolonged dose-dependently the oxidation lag time compared with the control. For the ex vivo study 24 volunteers consumed astaxanthin at doses of 1.8, 3.6, 14.4, 21.6 mg per day for 14 days. LDL lag time was longer in the groups who intaked astaxanthin compared with day 0, but there was no difference in oxidation of LDL in the control group. Our results provide evidence that consumption of marine animals producing astaxanthin inhibits LDL oxidation and possibly therefore contributes to the prevention of atherosclerosis.

Astaxanthin, oxidative stress, inflammation and cardiovascular disease

Robert G Fassett & Jeff S Coombes

It is accepted that oxidative stress and inflammation play an integral role in the pathophysiology of many chronic diseases including atherosclerotic cardiovascular disease. The xanthophyll carotenoid dietary supplement astaxanthin has demonstrated potential as an antioxidant and anti-inflammatory therapeutic agent in models of cardiovascular disease. There have been at least eight clinical studies conducted in over 180 humans using astaxanthin stress, inflammation or the cardiovascular system. There have been no adverse outcomes reported. Studies have demonstrated reduced markers of oxidative stress and inflammation and improved blood rheology. A larger number of experimental studies have been performed using astaxanthin. In particular, studies in a variety of animals using a model of myocardial ischemia and reperfusion have demonstrated protective effects from prior administration of astaxanthin both intravenously and orally. Future clinical studies and trials will help determine the efficacy of antioxidants such as astaxanthin on vascular structure, function oxidative stress and inflammation in a variety of patients at risk of , or with, established cardiovascular disease. These may lead to large intervention trials assessing cardiovascular morbidity and mortality.

Biochimica et Biophysica Acta 1768 (2007) 167–174

Differential effects of carotenoids on lipid peroxidation due to membrane interactions: X-ray diffraction analysis

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Robert F. Jacob a, R. Preston Mason a,c

Abstract
The biological benefits of certain carotenoids may be due to their potent antioxidant properties attributed to specific physico-chemical interactions with membranes. To test this hypothesis, we measured the effects of various carotenoids on rates of lipid peroxidation and correlated these findings with their membrane interactions, as determined by small angle X-ray diffraction approaches. The effects of the homochiral
carotenoids (astaxanthin, zeaxanthin, lutein, β-carotene, lycopene) on lipid hydroperoxide (LOOH) generation were evaluated in membranes enriched with polyunsaturated fatty acids. Apolar carotenoids, such as lycopene and β-carotene, disordered the membrane bilayer and showed a potent pro-oxidant effect (>85% increase in LOOH levels) while astaxanthin preserved membrane structure and exhibited significant antioxidant
activity (40% decrease in LOOH levels). These findings indicate distinct effects of carotenoids on lipid peroxidation due to membrane structure
changes. These contrasting effects of carotenoids on lipid peroxidation may explain differences in their biological activity.

Cardioprotective

Antioxid Redox Signal. 2003 Feb;5(1):139-44.

Astaxanthin limits exercise-induced skeletal and cardiac muscle damage in mice.

Aoi, et al, 2003

Dietary antioxidants may attenuate oxidative damage from strenuous exercise in various tissues. Beneficial effects of the antioxidant astaxanthin have been demonstrated in vitro, but not yet in vivo. We investigated the effect of dietary supplementation with astaxanthin on oxidative damage induced by strenuous exercise in mouse gastrocnemius and heart. C57BL/6 mice (7 weeks old) were divided into groups: rested control, intense exercise, and exercise with astaxanthin supplementation. After 3 weeks of exercise acclimation, both exercise groups ran on a treadmill at 28 m/min until exhaustion. Exercise-increased 4-hydroxy-2-nonenal-modified protein and 8-hydroxy-2'-deoxyguanosine in gastrocnemius and heart were blunted in the astaxanthin group. Increases in plasma creatine kinase activity, and in myeloperoxidase activity in gastrocnemius and heart, also were lessened by astaxanthin. Astaxanthin showed accumulation in gastrocnemius and heart from the 3 week supplementation. Astaxanthin can attenuate exercise-induced damage in mouse skeletal muscle and heart, including an associated neutrophil infiltration that induces further damage.

Cardioprotective

Mol Cell Biochem. 2005 Apr;272(1-2):221-7.

Acute and chronic administration of disodium disuccinate astaxanthin (Cardax) produces marked cardioprotection in dog hearts.

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Previous results from our laboratory have shown that a novel carotenoid derivative (disodium disuccinate astaxanthin; Cardax) produced dose-related reductions in myocardial infarct size (IS) in Sprague-Dawley rats when it was administered at any of three doses (25, 50 and 75 mg/kg, iv) on four consecutive days, followed by the acute infarct size study on day 5. Maximum salvage occurred at the highest dose (75 mg/kg) tested, and was shown as a 56% reduction in IS. In the present follow-up study, we used a more relevant large animal model, the dog, and looked at the effect of administering Cardax iv either acutely 2 h prior to occlusion (N = 8) or for 4 days at 50 mg/kg iv as previously done in the rat model (N = 6). The results were compared to a saline vehicle-treated group (N = 10). In all groups, dogs were subjected to 60 min of left anterior descending (LAD) coronary artery occlusion and 3 h of reperfusion. IS was determined using a triphenyltetrazolium chloride (TTZ) histochemical stain and was expressed as a percent of the area at risk (IS/AAR). IS/AAR was 20.9 +/- 1.6 % (mean +/- S.E.M.) in controls and was reduced to 11.0 +/- 1.7% (47.3% salvage; $p < 0.01$) in dogs treated only once iv at 2 h prior to occlusion, and 6.6 +/- 2.8% (68.4% salvage; $p < 0.001$) in dogs treated for 4 days. In the chronic treatment group, two of the three dogs with plasma concentrations of non-esterified astaxanthin above 1 microM had 0% IS/AAR (100% cardioprotection). These results suggest that Cardax has marked cardioprotective properties in both rodents and canines. Thus, Cardax may be a novel and powerful new means to prevent myocardial injury and/or necrosis associated with elective and/or urgent cardiac surgical interventions such as coronary angioplasty and stenting, as well as coronary artery bypass surgery (CABG).
PMID: 16010990 [PubMed - indexed for MEDLINE]

Cardioprotective

Biosci Biotechnol Biochem. 2007 Apr;71(4):893-9. Epub 2007 Apr 7.

Effects of astaxanthin in obese mice fed a high-fat diet.

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Laboratory of Nertraceuticals and Functional Foods Science, Graduate School of Marine Science and Technology, Tokyo University of Marine Science and Technology, Tokyo, Japan.

Astaxanthin is a natural antioxidant carotenoid that occurs in a wide variety of living organisms. We investigated the effects of astaxanthin supplementation in obese mice fed a high-fat diet. Astaxanthin inhibited the increases in body weight and weight of adipose tissue that result from feeding a high-fat diet. In addition, astaxanthin reduced liver weight, liver triglyceride, plasma triglyceride, and total cholesterol. These results suggest that astaxanthin might be of value in reducing the likelihood of obesity and metabolic syndrome in affluent societies.

Cardioprotective

Organo Oficial de la Sociedad Latinoamericana de Nutricion Vol.42 No4. 1992

The Effect of Canthaxanthin and Astaxanthin on Hypercholesterolemic on Rats

Enrique Murillo

Hypercholesterolemic effects of canthaxanthin and astaxanthin in rats. Three groups of male Wistar rats (130-140 g) were fed 30 days with a synthetic diets containing 0,1% of β-carotene, canthaxanthin and astaxanthin respectively. Another group was fed with a synthetic diet without carotenoids. The results shows that the β-carotene dies not induce change in plasma cholesterol (49, 7±3,6 mg/dl), but canthaxanthin and astaxanthin induce a significant increase in cholesterol concentration (92,1±3,6 and 66,1±5,1 mg/dl). This increase is noted mainly in the HDL fraction of the lipoproteins. Canthaxanthin has more affinity than astaxanthin for the liver, principal site of lipoproteins catabolism. The hipercholesterolemic effect of these xanthophylls is not related to reported mechanisms of carotenoids in mammalian, because β-carotene does not induce changes in plasma cholesterol.

Cardioprotective

Biol Pharm Bull S0989A 0918-6158 VOL.29;NO.4;PAGE.684-688 (J-STAGE)(2006)

Antihypertensive Potential and Mechanism of Action of Astaxanthin: III. Antioxidant and Histopathological Effects in Spontaneously Hypertensive Rats

HUSSEIN GHAZI HUSSEIN GHAZI GOTO HIROZO ODA SHINOBU SANKAWA USHIO MATSUMOTO KINZO (WATANABE HIROSHI

Abstract;We investigated the effects of a dietary astaxanthin (ASX-O) on oxidative parameters in spontaneously hypertensive rats (SHR), by determination of the level of nitric oxide (NO) end products nitrite/nitrate (NO2'-'/NO3'-') and lipid peroxidation in ASX-O-treated SHR. Oral administration of the ASX-O significantly reduced the plasma level of NO2'-'/NO3'-' compared to the control vehicle ($p<0.05$). The lipid peroxidation level, however, was reduced in both ASX-O- and olive oil-treated groups. We also analyzed the post-treatment effects of ASX-O on the vascular tissues by examining the changes in the aorta and coronary arteries and arterioles. The dietary ASX-O showed significant reduction in the elastin bands in the rat aorta ($p<0.05$). It also significantly decreased the [wall : lumen] aerial ratio of the coronary arteries. These results suggest that ASX-O can modulate the oxidative condition and may improve vascular elastin and arterial wall thickness in hypertension.

Cardioprotective

Biol Pharm Bull S0989A 0918-6158 VOL.28;NO.6;PAGE.967-971(2005)

Antihypertensive Potential and Mechanism of Action of Astaxanthin: II. Vascular Reactivity and Hemorheology in Spontaneously Hypertensive Rats

HUSSEIN GHAZI GOTO HIROZO ODA SHINOBU IGUCHI TOMOMI SANKAWA USHIO MATSUMOTO KINZO WATANABE HIROSHI

Abstract;The current study was designed to determine the effects of a dietary astaxanthin (ASX-O) on vascular reactivity in spontaneously hypertensive rats (SHR), in order to verify its antihypertensive action mechanism. We evaluated contractions induced by phenylephrine (Phe), angiotensin II (Ang II) and the xanthine/xanthine oxidase (Xan/XOD) system, and relaxations induced by sodium nitroprusside (SNP) as well as endothelium-dependent relaxations mediated by acetylcholine (ACh) in thoracic aorta of the SHR, with and without ASX-O intervention. We also investigated the effects of ASX-O on blood rheology using a microchannel array system. In this study, ASX-O showed a significant modulatory effect on nitric oxide (NO)-induced vasorelaxation by the NO-donor SNP ($p<0.05$). However, it did not show significant effects in restoring the impaired endothelium-dependent relaxation to ACh in the SHR. On the other hand, the constrictive effects by Phe, Ang II and Xan/XOD were ameliorated by ASX-O ($p<0.05$). ASX-O also demonstrated significant hemorheological effect by decreasing the microchannel transit time of whole blood. In conclusion, the results suggest that ASX-O may act in modulating the blood fluidity in hypertension, and that the antihypertensive effects of ASX-O may be exerted through mechanisms including normalization of the sensitivity of the adrenoceptor sympathetic pathway, particularly [alpha]-adrenoceptors, and by restoration of the vascular tone through attenuation of the Ang II- and reactive oxygen species (ROS)-induced vasoconstriction.

Cardioprotective

JOURNAL OF FUNCTIONAL FOODS 1 (2009) 13–22

Astaxanthin lowers blood pressure and lessens the activity of the renin-angiotensin system in Zucker Fatty Rats

Harry G. Preussa,*, Bobby Echarda, Debasis Bagchib, Nicholas V. Perriconec, Eiji Yamashita

The ability of astaxanthin to favorably influence the renin-angiotensin system (RAS), blood pressure (BP), and metabolic parameters in Zucker Fatty Rats (ZFR) was examined. In separate experiments, 96 ZFR were equally divided into four groups: control, captopril (30 mg/kg), low astaxanthin (5 mg/kg) and high astaxanthin (25 mg/kg). RAS and insulin systems were examined following recovery from heat stress. RAS was lower in test groups; however, there was no evidence of enhanced insulin sensitivity. Test groups decreased SBP (systolic blood pressure) significantly compared to the control. The tests carried out suggested that RAS was involved in the ability of astaxanthin to lower BP. Astaxanthin at high dosage influenced circulating TNF-a and MCP-1 and lessened fat oxidation in liver and kidneys. Thus, astaxanthin may be considered as a good stress reducer with regards to heat stress. Astaxanthin's effects on RAS indicate it might overcome perturbations associated with increased activity, especially those related to the cardiovascular system.

Cardioprotective

J Mol Cell Cardiol. 2004 Nov;37(5):969-78.

Alpha-tocopherol and astaxanthin decrease macrophage infiltration, apoptosis and vulnerability in atheroma of hyperlipidaemic rabbits.

The composition of atherosclerotic plaques, not just macroscopical lesion size, has been implicated in their susceptibility to rupture and the risk of thrombus formation. By focusing on the quality of lipids, macrophages, apoptosis, collagen, metalloproteinase expression and plaque integrity, we evaluated the possible anti-atherosclerotic effect of the antioxidants alpha-tocopherol and astaxanthin in Watanabe heritable hyperlipidemic (WHHL) rabbits. Thirty-one WHHL rabbits were divided into three groups and were fed a standard diet, as controls (N =10), or a standard diet with the addition of 500 mg alpha-tocopherol per kg feed (N =11) or 100 mg astaxanthin per kg feed (N =10) for 24 weeks. We found that both antioxidants, particularly astaxanthin, significantly decreased macrophage infiltration in the plaques although they did not affect lipid accumulation. All lesions in the astaxanthin-treated rabbits were classified as early plaques according to the distribution of collagen and smooth muscle cells. Both antioxidants also improved plaque stability and significantly diminished apoptosis, which mainly occurred in macrophages, matrix metalloproteinase three expressions and plaque ruptures. Although neither antioxidant altered the positive correlations between the lesion size and lipid accumulation, the lesion size and apoptosis were only positively correlated in the control group. Astaxanthin and alpha-tocopherol may improve plaque stability by decreasing macrophage infiltration and apoptosis in this atherosclerotic setting. Apoptosis reduction by alpha-tocopherol and astaxanthin may be a new anti-atherogenic property of these antioxidants.

Cardioprotective

J of the Pharmaceutical Society of Japan VOL.126;NO.Suppl.3;PAGE.16-19(2006)

PREVENTION BY ASTAXANTHIN OF LIFE STYLE DISEASES: EXPERIMENTAL EVIDENCES

WATANABE HIROSHI; HUSSEIN GHAZI; GOTO HIROZO; NAKAGAWA TAKAKO; MATSUMOTO KINZO; SANKAWA USHIO

Astaxanthin (ASX), a red-orange carotenoid pigment, is a powerful antioxidant that occurs naturally in a wide variety of living organisms. We investigated the effect of ASX on the incidence of stroke, hypertension, and hyperglycemia in rats. Repeated ASX (50 mg/kg/day, p.o.) inhibited the incidence of stroke in SHR-stroke prone (SP). Pretreatment with 50 mg/kg/day of ASX for a week produced anti-hypertensive effect in awaked SHR. In the isolated aorta, ASX inhibited the vascular contraction induced by PGF2.ALPHA.. Pretreatment with L-NAME (10'-4'M) ameliorated the inhibitory effect of ASX. ASX produced a significant reduction in the elastin bands and diminished the wall thickness in the SHR aorta. Fifty mg/kg of ASX for 18 weeks caused a significant decrease in the blood glucose in SHR/ND mcr-cp (cp/cp). ASX (50 mg/kg) produced a tendency to improve the learning behavior deficit induced by the brain ischemia in mice. These results suggest that ASX may exert beneficial effects for the protection against lifestyle related diseases.

Cardioprotective

J Cardiovasc Pharmacol. 2006 May;47 Suppl 1:S7-S14.

Rofecoxib Increases Susceptibility of Human LDL and Membrane Lipids to Oxidative Damage: A Mechanism of Cardiotoxicity.

Preston Mason R, **Walter MF**, **McNulty HP**, **Lockwood SF**, **Byun J**, **Day CA**, **Jacob RF**.

*Cardiovascular Division, Brigham and Women's Hospital, Harvard Medical School, Boston, MA daggerElucida Research LLC, Beverly, MA double daggerAtlanta VA Medical Center, Atlanta, GA section signCardax Pharmaceuticals, Inc, Aiea, HI.

Clinical investigations have demonstrated a relationship between the extended use of rofecoxib and the increased risk for atherothrombotic events. This has led to the removal of rofecoxib from the market and concern over the cardiovascular safety of other cyclooxygenase (COX)-2 selective agents. Experimental findings from independent laboratories now indicate that the cardiotoxicity of rofecoxib may not be a class effect but because of its intrinsic chemical properties. Specifically, rofecoxib has been shown to increase the susceptibility of human low-density lipoprotein and cellular membrane lipids to oxidative modification, a contributing factor to plaque instability and thrombus formation. Independently of COX-2 inhibition, rofecoxib also promoted the nonenzymatic formation of isoprostanes and reactive aldehydes from biologic lipids. The basis for these observations is that rofecoxib alters lipid structure and readily forms a reactive maleic anhydride in the presence of oxygen. By contrast, other selective (celecoxib, valdecoxib) and nonselective (naproxen, diclofenac) inhibitors did not influence rates of low-density lipoprotein and membrane lipid oxidation. We have now further confirmed these findings by demonstrating that the prooxidant activity of rofecoxib can be blocked by the potent antioxidant astaxanthin in homochiral form (all-trans 3S, 3'S). These findings provide a mechanistic rationale for differences in cardiovascular risk among COX-selective inhibitors because of their intrinsic physicochemical properties.

Cardioprotective

Pharmacol Res. 2010 Sep 22. [Epub ahead of print]

Astaxanthin-enriched-diet reduces blood pressure and improves cardiovascular parameters in spontaneously hypertensive rats.

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Abstract

The aim of this study was to investigate the effects of astaxanthin-enriched diet on blood pressure, cardiac hypertrophy, both vascular structure and function and superoxide (O(2)(-)) production in spontaneously hypertensive rats (SHR). Twelve-week-old SHR were treated for 8 weeks with an astaxanthin-enriched diet (75 or 200mg/kg body weight per day). Systolic blood pressure was monitorized periodically during the study by the tail cuff method. At the end of the study animals were sacrificed and heart, kidneys and aorta were removed. Left ventricular weight/body weight ratio was used as left ventricular hypertrophy index (LVH). Vascular function and structure were studied in conductance (aortic rings) and resistance (renal vascular bed) arteries. Also O(2)(-) production was evaluated by lucigenin-enhanced chemiluminescence. Systolic blood pressure was lower in astaxanthin-treated groups than the control group from the first week of treatment, and LVH was significantly reduced. Astaxanthin improved endothelial function on resistance arteries, but had no effect on aorta. These effects were accompanied by a decrease in oxidative stress and improvements in NO bioavailability. Taken together, these results show that diet supplemented with astaxanthin has beneficial effects on hypertension, by decreasing blood pressure values, improving cardiovascular remodeling and oxidative stress.

PMID: 20868751 [PubMed - as supplied by publisher]

Cardioprotective

Future Cardiol. 2009 Jul;5(4):333-42.

Astaxanthin, oxidative stress, inflammation and cardiovascular disease.

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Abstract

It is accepted that oxidative stress and inflammation play an integral role in the pathophysiology of many chronic diseases including atherosclerotic cardiovascular disease. The xanthophyll carotenoid dietary supplement astaxanthin has demonstrated potential as an antioxidant and anti-inflammatory therapeutic agent in models of cardiovascular disease. There have been at least eight clinical studies conducted in over 180 humans using astaxanthin to assess its safety, bioavailability and clinical aspects relevant to oxidative stress, inflammation or the cardiovascular system. There have been no adverse outcomes reported. Studies have demonstrated reduced markers of oxidative stress and inflammation and improved blood rheology. A larger number of experimental studies have been performed using astaxanthin. In particular, studies in a variety of animals using a model of myocardial ischemia and reperfusion have demonstrated protective effects from prior administration of astaxanthin both intravenously and orally. Future clinical studies and trials will help determine the efficacy of antioxidants such as astaxanthin on vascular structure, function, oxidative stress and inflammation in a variety of patients at risk of, or with, established cardiovascular disease. These may lead to large intervention trials assessing cardiovascular morbidity and mortality.

PMID: 19656058 [PubMed - indexed for MEDLINE]

Eur J Nutr. 2010 Mar;49(2):119-26. Epub 2009 Sep 26.

Astaxanthin suppresses scavenger receptor expression and matrix metalloproteinase activity in macrophages.

Kishimoto Y, Tani M, Uto-Kondo H, Iizuka M, Saita E, Sone H, Kurata H, Kondo K.

Institute of Environmental Science for Human Life, Ochanomizu University, Tokyo, Japan.

Abstract

BACKGROUND: Astaxanthin is a red carotenoid pigment which has significant potential for antioxidant activity. The macrophages in atherosclerotic lesions, known as activated macrophages, express scavenger receptors responsible for the clearance of pathogenic lipoproteins. In addition, the expression and secretion of proteolytic enzymes, matrix metalloproteinases (MMPs), and pro-inflammatory cytokines are remarkably promoted in activated macrophages.

AIM OF THE STUDY: In this study, we investigated the effects of astaxanthin on the expression of scavenger receptors, MMPs, and pro-inflammatory cytokines in macrophages.

METHODS: THP-1 macrophages were incubated with 5-10 microM astaxanthin for 24 h. The expression levels of scavenger receptors, MMPs, and pro-inflammatory cytokines were determined by Western blot analysis or real-time RT-PCR. The MMP-9 and -2 activities were examined by gelatin zymography and total MMP activity was measured by fluorometry.

RESULTS: We found that astaxanthin remarkably decreased the class A scavenger receptor and CD36 expression in the protein and mRNA levels. Astaxanthin also reduced MMP-1, -2, -3, -9, -12, and -14 activity and expression. The mRNA expression of tumor necrosis factor-alpha, interleukin-1beta, interleukin-6, inducible nitric oxide synthase, and cyclooxygenase-2 were significantly suppressed by astaxanthin. Furthermore, astaxanthin inhibited the phosphorylation of nuclear factor-kappaB.

CONCLUSIONS: These results indicate that astaxanthin has inhibitory effects on macrophage activation, such as scavenger receptors up-regulation, MMPs activation, and pro-inflammatory cytokines secretion.

PMID: 19784539 [PubMed - indexed for MEDLINE]

Cardioprotective

Thromb Res. 2010 Oct;126(4):299-305. Epub 2010 Aug 21.

Novel astaxanthin prodrug (CDX-085) attenuates thrombosis in a mouse model.

Khan SK, Malinski T, Mason RP, Kubant R, Jacob RF, Fujioka K, Denstaedt SJ, King TJ, Jackson HL, Hieber AD, Lockwood SF, Goodin TH, Pashkow FJ, Bodary PF.

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Abstract

BACKGROUND: Cardiovascular disease remains the leading cause of morbidity and premature mortality in most industrialized countries as well as in developing nations. A pro-oxidative state appears to promote and/or exacerbate vascular disease complications. Furthermore, a state of low-grade chronic inflammation can promote increased oxidative stress and lead to endothelial cell and platelet dysfunction ultimately contributing to thrombogenesis.

OBJECTIVES: In this study, the effect of a proprietary astaxanthin prodrug (CDX-085) on thrombus formation was investigated using a mouse model of arterial thrombosis. The influence of free astaxanthin, the active drug of CDX-085, on human endothelial cells and rat platelets was evaluated to investigate potential mechanisms of action.

METHODS AND RESULTS: Oral administration of CDX-085 (0.4% in chow, approximately 500 mg/kg/day) to 6-8 week old C57BL/6 male mice for 14 days resulted in significant levels of free astaxanthin in the plasma, liver, heart and platelets. When compared to control mice, the CDX-085 fed group exhibited significant increases in basal arterial blood flow and significant delays in occlusive thrombus formation following the onset of vascular endothelial injury. Primary human umbilical vein endothelial cells (HUVECs) and platelets isolated from Wistar-Kyoto rats treated with free astaxanthin demonstrated significantly increased levels of released nitric oxide (NO) and significantly decreased peroxynitrite (ONOO-) levels.

CONCLUSION: Observations of increased NO and decreased ONOO- levels in endothelial cells and platelets support a potential mechanism of action for astaxanthin (CDX-085 active drug). These studies support the potential of CDX-085 and its metabolite astaxanthin in the treatment or prevention of thrombotic cardiovascular complications.

PMID: 20728920 [PubMed - in process]

Cardioprotective

Anticancer Res. 2010 Jul;30(7):2721-5.

Effect of astaxanthin supplementation on inflammation and cardiac function in BALB/c mice.

Nakao R, Nelson OL, Park JS, Mathison BD, Thompson PA, Chew BP.

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Abstract

Astaxanthin is an antioxidant with immunomodulatory, anti-inflammatory and anticancer properties. This study evaluated the use of dietary astaxanthin to decrease oxidative stress and improve cardiac function, thereby providing a potential cardioprotective supplement. Female BALB/c mice (8 weeks of age) were fed a semi-synthetic diet containing 0, 0.02 or 0.08% astaxanthin for 8 weeks. Cardiac function was assessed by echocardiography bi-weekly, and blood and tissue samples were collected at 8 weeks. Plasma astaxanthin concentrations increased ($p<0.05$) dose-dependently to 0.5 and 4 mumol/l in the astaxanthin-supplemented mice. Blood glutathione concentrations and lymphocyte mitochondrial membrane potential were not significantly affected by astaxanthin treatment. However, mice fed 0.08% astaxanthin had higher ($p<0.05$) heart mitochondrial membrane potential and contractility index compared to the control group. These results support the possible use of dietary astaxanthin for cardiac protection.

PMID: 20683004 [PubMed - indexed for MEDLINE]

Cardioprotective

J Cardiovasc Pharmacol Ther. 2009 Dec;14(4):314-22. Epub 2009 Oct 21.

Astaxanthin reduces oxidative stress, but not aortic damage in atherosclerotic rabbits.

Augusti PR, Conterato GM, Somacal S, Sobieski R, Quatrin A, Maurer L, Rocha MP, Denardin IT, Emanuelli T.

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Abstract

We evaluated whether carotenoid astaxanthin (ASX) could prevent oxidative and atherosclerotic damage in rabbits. Rabbits received regular chow (control) or an atherogenic diet (1% cholesterol) alone or supplemented with 50, 100, and 500 mg% ASX for 60 days (n = 5-9 per group). The atherogenic diet increased the serum cholesterol levels and the ratio of the intima/media area in the aortic arch. These changes were not prevented by ASX. Atherosclerotic rabbits showed increased aortic lipid peroxidation and nonprotein thiol group (NPSH) levels along with inhibition of glutathione peroxidase (GSH-Px). All ASX doses attenuated lipid peroxidation and the increase in NPSH but not the inhibition of GSH-Px. Aortic superoxide dismutase (SOD), catalase (CAT), and thioredoxin reductase (TrxR) activities were enhanced in atherosclerotic rabbits. Although all ASX doses prevented the increase in SOD activity, only 100 and 500 mg% ASX prevented the increase in CAT activity. Furthermore, these same doses partially prevented the increase in TrxR activity, while 50 mg% ASX completely prevented the effects of the atherogenic diet on this enzyme. However, ASX did not attenuate the hypercholesterolemia or the atherosclerotic lesions caused by the atherogenic diet at any of the doses evaluated. Our results indicate that although ASX did not prevent hypercholesterolemia or atherosclerotic lesions, it could play a beneficial role by preventing lipid peroxidation and changes in antioxidant enzyme activities.

PMID: 19846890 [PubMed - indexed for MEDLINE]

Cardioprotective

Curr Atheroscler Rep. 2009 Nov;11(6):434-9.

Carotenoids and cardiovascular disease.

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Abstract

Carotenoids are a class of natural fat-soluble pigments found principally in plants. They have potential antioxidant biological properties due to their chemical structure and interaction with biological membranes. The most abundant carotenoids in the diet are beta-carotene, lycopene, lutein, beta-cryptoxanthin, zeaxanthin, and astaxanthin. Numerous epidemiologic studies have supported the hypothesis that antioxidants could be used as an inexpensive means of prevention, and possibly treatment, of cardiovascular diseases, even though findings from interventional trials have been mixed, with some positive findings, many null findings, and some suggestion of harm in certain high-risk populations. Recent smaller interventional studies with carefully chosen populations, such as those under high levels of oxidative stress, have yielded largely positive results. This suggests that we need more hypothesis-driven and rigorous clinical trial designs. The aim of this review is to examine the published studies about the use of carotenoids, especially lycopene and astaxanthin, in the treatment of cardiovascular diseases.

PMID: 19852884 [PubMed - indexed for MEDLINE]

Immunity

Nutr Metab (Lond). 2010 Mar 5;7:18.

Astaxanthin decreased oxidative stress and inflammation and enhanced immune response in humans.

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ABSTRACT:

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 Thelper, Tcytotoxic 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.

PMID: 20205737 [PubMed - in process]PMCID: PMC2845588

Immunity

Experimental Biology Saturday, April 17, 2004
Abstract #341.4

Immune stimulating action of dietary astaxanthin in humans

J. Park, J. Chyun, Y. Kim, L. Line, M. Maloney and B. Chew

We studied the role of dietary astaxanthin on immunity and oxidative status. Female subjects (21.5 yr) with no history of major diseases received 0, 2, or 8 mg astaxanthin (n = 14) daily for 8 wk in a double-blind, placebo controlled study. Blood was drawn on wk 0, 4 and 8. The tuberculin test was assessed on wk 8. Plasma astaxanthin was undetectable prior to feeding but increased ($P < 0.01$) dose-dependently on wk 4 and 8. Dietary astaxanthin stimulated concanavalin A-, phytohemagglutinin- and pokeweed mitogen-induced lymphoproliferation and increased NK cell cytotoxic activity. In addition, astaxanthin also increased the proportion of total T cells and B cells, but did not influence the populations of Th, Tc or NK cells or the ratio of Th:Tc cells. The frequency of cells expressing LFA-1 marker was higher in subjects given 2 mg (42.1%) but not those given 8 mg (30.6%) astaxanthin compare to control (31.8%) on wk 8. No similar dietary effect was observed with ICAM-1 or LFA-3 expression. Subjects fed 2 mg but not those fed 8 mg astaxanthin had higher DTH response than unsupplemented controls. Dietary astaxanthin dramatically decreased blood DNA damage (8-oxodeoxyguanosine) after 4 wk of feeding but did not influence lipid peroxidation in plasma. Therefore, dietary astaxanthin enhanced immune response and decrease DNA damage in human subjects.

Int J Immunopharmacol. 1996 Dec;18(12):753-8.

Possible immunomodulating activities of carotenoids in in vitro cell culture experiments.

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Immunomodulating activities of beta-carotene and carotene-associated carotenoids such as canthaxanthin (beta, beta-carotene-4,4 dione) and astaxanthin (3,3'-dihydroxyl beta, beta-carotene 4,4-dione) were analyzed by in vitro cell culture experiments. (i) beta-Carotene, canthaxanthin and astaxanthin caused significant stimulatory effects on the cell proliferative response of spleen cells and thymocytes from BALB/c mice at the concentrations of 2 x 10(-8) to 10(-7) M, although they showed the activities different from each other. (ii) Astaxanthin exhibited the highest activity on the polyclonal antibody (immunoglobulin M and G) production of murine spleen cells at the concentrations of 2 x 10(-8) to 10(-7) M but beta-carotene did not cause a significant effect at a low concentration (2 x 10(-8) M) although stimulated at a high concentration (2 x 10(-7) M). Canthaxanthin expressed moderate activities at the same concentrations. (iii) All tested carotenoids significantly enhanced the release of interleukin-1 alpha and tumor necrosis factor-alpha from murine peritoneal adherent cells at the concentrations of 2 x 10(-8) to 10(-7) M and the ranks of cytokine-inducing activities were astaxanthin > canthaxanthin > beta-carotene. These results indicate that carotenoids such as beta-carotene, canthaxanthin and astaxanthin have possible immunomodulating activities to enhance the proliferation and functions of murine immunocompetent cells.

PMID: 9172019 [PubMed - indexed for MEDLINE]

Nutr Cancer. 1996;26(3):313-24.

Effects of various carotenoids on cloned, effector-stage T-helper cell activity.

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Astaxanthin, a carotenoid without provitamin A activity, enhances murine T-helper (Th) cell clone-mediated antibody (Ab) production with suboptimal antigen (Ag) challenges. It also suppresses interferon-gamma (IFN-gamma) production by cloned murine Th1 cells. beta-Carotene is less effective than astaxanthin. This study evaluates the effects of various carotenoids with various relative polarity, provitamin A activity, and antioxidant activity. Carotenoids tested include astaxanthin, cantaxanthin, zeaxanthin, lutein, and lycopene, and their effects were tested at a concentration at which astaxanthin's effect was most potent. A.E7 and CDC35 cells are used as representative type 1 and type 2 Th cell (Th1 and Th2) clones, respectively. In the Th1 clone, astaxanthin, but not other carotenoids, suppressed IFN-gamma production and increased the number of Ab-secreting cells with the use of primed spleen cells. With cultures of Th1 cells and unprimed spleen cells, astaxanthin and zeaxanthin augmented the number of immunoglobulin M Ab-secreting cells. In the cultures of Th2 clone and primed spleen cells, astaxanthin, but not other carotenoids, enhanced the number of Ab-secreting cells. With unprimed spleen cells, lycopene suppressed Th2 clone-mediated Ab production. Interleukin-5 production by the Th2 clone was not significantly altered with the carotenoids tested, irrespective of the use of unprimed or primed spleen cells. Carotenoid actions on Th cells may vary in each carotenoid and do not seem to be closely associated with carotenoid antioxidant activity or relative polarity.

Publication Types:

PMID: 8910913 [PubMed - indexed for MEDLINE]

Anticancer Res. 1999 Nov-Dec;19(6B):5223-7.

Dietary beta-carotene and astaxanthin but not canthaxanthin stimulate splenocyte function in mice.

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The in vivo modulatory effect of beta-carotene, astaxanthin and canthaxanthin on lymphocyte function was investigated. Female BALB/c mice (8 wk old) were fed a basal diet containing 0, 0.1% or 0.4% beta-carotene, astaxanthin or canthaxanthin for 0, 2 or 4 wk (n = 8/diet/period). Splenic lymphocytes were isolated and mitogen-stimulated proliferation, IL-2 production and lymphocyte cytotoxicity were assessed. Body weight and feed intake were not different among dietary treatments. Plasma carotenoids were undetectable in unsupplemented mice but concentrations of the respective carotenoids were elevated in mice fed 0.1 or 0.4% beta-carotene (0.22 and 0.39 mumol/L), astaxanthin (16.4 and 50.2 mumol/L) and canthaxanthin (5.00 and 7.02 mumol/L) respectively. Mice fed both dietary levels of beta-carotene and astaxanthin had enhanced phytohemagglutinin-induced lymphoblastogenesis compared to unsupplemented mice ($P < 0.03$). No treatment difference was detected with concanavalin A- or lipopolysaccharide-induced lympho-proliferation nor with IL-2 production ($P < 0.05$). Astaxanthin (0.1%) also enhanced lymphocyte cytotoxic activity ($P < 0.08$). In contrast, canthaxanthin did not significantly influence any of the lymphocyte functions measured. Results indicate that beta-carotene and astaxanthin but not canthaxanthin exert enhanced splenic lymphocyte function in mice.

Br Poult Sci. 2007 Feb;48(1):90-7.

Effect of dietary supplementation of astaxanthin by Phaffia rhodozyma on lipid peroxidation, drug metabolism and some immunological variables in male broiler chicks fed on diets with or without oxidised fat.

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1. Effects of dietary supplementation of astaxanthin (Ax) provided from Phaffia rhodozyma on lipid peroxidation, hepatic drug metabolism, antibody titres to sheep red blood cells (SRBC) and splenocyte proliferation to mitogens were determined in male broiler chicks. 2. Chicks, one week old, were given diets with or without oxidised fat (0 or 3.7 meq of peroxide value (POV)/kg diet) and/or Ax (0 or 100 mg/kg diet) for 14 d, ad libitum. 3. Lipid peroxidation, estimated by 2-thiobarbituric acid reactants values in liver, spleen, heart, plasma and hepatic microsomes, were increased by feeding a diet containing oxidised fat ($P<0.05$) but were not affected by Ax feeding. 4. Cytochrome P-450 contents in hepatic microsome tended to be increased by feeding Ax. 5. Anti-SRBC titre was not affected by oxidised fat or Ax feeding, while plasma immunogloblin (Ig) G concentration was increased by Ax feeding but was not affected by oxidised fat feeding. 6. When chicks were fed on the diet without oxidised fat, Ax enhanced splenocyte proliferation stimulated by both concanavalin A and pokeweed mitogen, while in chicks fed on a diet containing oxidised fat, Ax reduced the proliferation ($P<0.01$ for Ax and oxidised fat interaction). 7. The results indicated that dietary supplementation of Ax from Phaffia rhodozyma had an impact on T cell proliferation and Ig G production as a part of acquired immunity, but was not effective in preventing lipid peroxidation in male broiler chicks.

PMID: 17364546 [PubMed - indexed for MEDLINE]

Crit Rev Food Sci Nutr. 2006;46(2):185-96.

Astaxanthin: a review of its chemistry and applications.

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Astaxanthin is a carotenoid widely used in salmonid and crustacean aquaculture to provide the pink color characteristic of that species. This application has been well documented for over two decades and is currently the major market driver for the pigment. Additionally, astaxanthin also plays a key role as an intermediary in reproductive processes. Synthetic astaxanthin dominates the world market but recent interest in natural sources of the pigment has increased substantially. Common sources of natural astaxanthin are the green algae Haematococcus pluvialis, the red yeast, Phaffia rhodozyma, as well as crustacean byproducts. Astaxanthin possesses an unusual antioxidant activity which has caused a surge in the nutraceutical market for the encapsulated product. Also, health benefits such as cardiovascular disease prevention, immune system boosting, bioactivity against Helycobacter pylori, and cataract prevention, have been associated with astaxanthin consumption. Research on the health benefits of astaxanthin is very recent and has mostly been performed in vitro or at the pre-clinical level with humans. This paper reviews the current available evidence regarding astaxanthin chemistry and its potential beneficial effects in humans.

Publication Types:

PMID: 16431409 [PubMed - indexed for MEDLINE]

Fish Shellfish Immunol. 2004 Apr;16(4):527-37.

Enhancement of innate immunity in rainbow trout (Oncorhynchus mykiss Walbaum) associated with dietary intake of carotenoids from natural products.

Amar EC, **Kiron V**, **Satoh S**, **Watanabe T**.

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The effects of orally administered carotenoids from natural sources on the non-specific defense mechanisms of rainbow trout were evaluated in a nine-week feeding trial. Fish were fed four diets containing either beta-carotene or astaxanthin at 100 and 200 mg kg-1 from the marine algae Dunaliella salina and red yeast Phaffia rhodozyma, respectively, and a control diet containing no supplemented carotenoids. Specific growth rate and feed:gain ratio were not affected by dietary carotenoid supplementation. Among the humoral factors, serum alternative complement activity increased significantly in all carotenoid supplemented groups when compared to the control. On the other hand, serum lysozyme activity increased in the Dunaliella group but not in the Phaffia group, whereas plasma total immunoglobulin levels were not altered by the feeding treatments. As for the cellular responses, the superoxide anion production from the head kidney remained unchanged while the phagocytic rate and index in all supplemented groups were significantly higher than those of the control. These findings demonstrate that dietary carotenoids from both D. salina and P. rhodozyma can modulate some of the innate defense mechanisms in rainbow trout.

Publication Types:

PMID: 15123294 [PubMed - indexed for MEDLINE]

J Nutr. 2004 Jan;134(1):257S-261S.

Carotenoid action on the immune response.

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Early studies demonstrating the ability of dietary carotenes to prevent infections have left open the possibility that the action of these carotenoids may be through their prior conversion to vitamin A. Subsequent studies to demonstrate the specific action of dietary carotenoids have used carotenoids without provitamin A activity such as lutein, canthaxanthin, lycopene and astaxanthin. In fact, these nonprovitamin A carotenoids were as active, and at times more active, than beta-carotene in enhancing cell-mediated and humoral immune response in animals and humans. Another approach to study the possible specific role of dietary carotenoids has used animals that are inefficient converters of carotenoids to vitamin A, for example the domestic cat. Results have similarly shown immuno-enhancement by nonprovitamin A carotenoids, based either on the relative activity or on the type of immune response affected compared to beta-carotene. Certain carotenoids, acting as antioxidants, can potentially reduce the toxic effects of reactive oxygen species (ROS). These ROS, and therefore carotenoids, have been implicated in the etiology of diseases such as cancer, cardiovascular and neurodegenerative diseases and aging. Recent studies on the role of carotenoids in gene regulation, apoptosis and angiogenesis have advanced our knowledge on the possible mechanism by which carotenoids regulate immune function and cancer.

Publication Types:

PMID: 14704330 [PubMed - indexed for MEDLINE]

J Nutr. 1995 Oct;125(10):2483-92.

Astaxanthin, a carotenoid without vitamin A activity, augments antibody responses in cultures including T-helper cell clones and suboptimal doses of antigen.

Jyonouchi H, **Sun S**, **Tomita Y**, **Gross MD**.

Department of Pediatrics, School of Medicine, University of Minnesota, Minneapolis 55455, USA.

Astaxanthin, a carotenoid without vitamin A activity, enhances T-dependent antigen (Ag)-specific humoral immune responses. We examined carotenoid actions on T-helper (Th) cell activity in a direct manner with reconstitution experiments; spleen Th cells were replaced with Ag-specific Type 1 and Type 2 (Th1 and Th2) Th cell clones. The Ag for the Th1 and Th2 clones were pigeon cytochrome C and rabbit gamma-globulin, respectively. Astaxanthin and beta-carotene augmented the number of IgM antibody (Ab)-secreting cells when unprimed B cells were incubated with Th clones and stimulated with suboptimal doses of Ag specific for each Th clone. The number of IgG Ab-secreting cells were greater with use of in vivo primed B cells than with unprimed B cells in both Th clones. Astaxanthin but not beta-carotene augmented the number of IgG Ab-secreting cells when primed B cells and Th cell clones were stimulated with suboptimal doses of Ag specific for each Th clone. In the presence of optimal doses of Ag for each Th clone, neither carotenoid augmented the number of Ab-secreting cells. Astaxanthin and beta-carotene may enhance the actions of both Th1 and Th2 cells for humoral immune responses with suboptimal Ag challenges; certain carotenoids may help maintain Ag-mediated immune responses at optimal levels.

Publication Types:

PMID: 7562082 [PubMed - indexed for MEDLINE]

Nutr Cancer. 1995;23(2):171-83.

Effect of carotenoids on in vitro immunoglobulin production by human peripheral blood mononuclear cells: astaxanthin, a carotenoid without vitamin A activity, enhances in vitro immunoglobulin production in response to a T-dependent stimulant and antigen.

Jyonouchi H, **Sun S**, **Gross M**.

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The effect of carotenoids on in vitro immunoglobulin (Ig) production by peripheral blood mononuclear cells (PBMNC) was examined by employing blood samples from adult volunteers and full-term newborn babies (umbilical cord blood). Under carotenoid-supplemented culture conditions, cells were stimulated by polyclonal stimulants, neoantigens, and a recall antigen (Ag), and IgM, IgA, and IgG levels in the culture supernatant were measured. Beta-carotene and astaxanthin were used as representatives of carotenoids with and without vitamin A activity, respectively. Astaxanthin enhanced IgM production in response to T-dependent Ag (TD-Ag) and a T-dependent polyclonal stimulant. Astaxanthin also augmented IgG production in response to a recall Ag. IgA production without supplemental carotenoids was negligible for all stimuli. However, in carotenoid-supplemented cultures, IgA production was significantly higher in response to a T-dependent polyclonal stimulant than in unsupplemented cultures. IgM and IgA production was augmented at 10(-8) mol/l astaxanthin, whereas astaxanthin enhanced IgG production in response to a recall Ag at 10(-10)-10(-9) mol/l. Similar enhancing actions of astaxanthin on IgM production were observed in cord blood mononuclear cells (CBMNC), although CBMNC produced less IgM than adult PBMNC. Beta-carotene did not have a significant effect on human Ig production. The carotenoid actions were not demonstrated under serum-free culture conditions; serum is essential for solubilization of carotenoids. In summary, this study has shown for the first time that astaxanthin, a carotenoid without vitamin A activity, enhances human Ig production in response to T-dependent stimuli.

Publication Types:

Nutr Cancer. 1994;21(1):47-58.

Immunomodulating actions of carotenoids: enhancement of in vivo and in vitro antibody production to T-dependent antigens.

Jyonouchi H, **Zhang L**, **Gross M**, **Tomita Y**.

Department of Pediatrics, University of Minnesota, Minneapolis 55455.

Previously, we demonstrated an enhancement of in vitro antibody (Ab) production in response to T-dependent antigens (TD-Ag) by astaxanthin, a carotenoid without vitamin A activity. The effects of beta-carotene, a carotenoid with vitamin A activity, and lutein, another carotenoid without vitamin A activity, on in vitro Ab production were examined with spleen cells from young and old B6 mice. In addition, the in vivo effects of lutein, astaxanthin, and beta-carotene on Ab production were studied in young and old B6 mice. Lutein, but not beta-carotene, enhanced in vitro Ab production in response to TD-Ags. The depletion of T-helper cells prevented the enhancement of Ab production by lutein and astaxanthin. In vivo Ab production in response to TD-Ag was significantly enhanced by lutein, astaxanthin, and beta-carotene. The numbers of immunoglobulin M- and G-secreting cells also increased in vivo with the administration of these carotenoids when mice were primed with TD-Ags. Antibody production in response to TD-Ags in vivo and in vitro was significantly lower in old than in young B6 mice. Astaxanthin supplements partially restored decreased in vivo Ab production in response to TD-Ags in old B6 mice. Lutein and beta-carotene also enhanced in vivo Ab production in response to TD-Ags in old B6 mice, although to a lesser extent than did astaxanthin. However, none of the carotenoids had an effect on in vivo or in vitro Ab production in response to T-independent antigen. These results indicate significant immunomodulating actions of carotenoids for humoral immune responses to TD-Ags and suggest that carotenoid supplementation may be beneficial in restoring humoral immune responses in older animals.

Publication Types:

PMID: 8183722 [PubMed - indexed for MEDLINE]

Nutr Cancer. 1993;19(3):269-80.

Studies of immunomodulating actions of carotenoids. II. Astaxanthin enhances in vitro antibody production to T-dependent antigens without facilitating polyclonal B-cell activation.

Jyonouchi H, **Zhang L**, **Tomita Y**.

Department of Pediatrics, University of Minnesota, Minneapolis 55455.

Previously we have shown that astaxanthin, a carotenoid without provitamin A activity, enhances in vitro antibody (Ab) production to sheep red blood cells in normal B6 mice. In this study, we further attempted to examine the mechanisms of this enhancing action of carotenoids on specific Ab production in vitro in relation to different antigen (Ag) stimuli, cytokine production, and T- and B-cell interactions in both normal and autoimmune strains of mice. When the actions of carotenoids were tested in normal strains of mice, we found that astaxanthin enhanced in vitro Ab production to T cell-dependent Ag, but not to T-independent Ag, and did not augment total immunoglobulin production. Astaxanthin exerted maximum enhancing actions when it was present at the initial period of Ag priming. This action of astaxanthin was abolished when T cells were depleted from spleen cell suspensions and appeared to require direct interactions between T and B cells. The results also indicated that carotenoids may modulate the production of interferon-tau in this assay system. When the actions of carotenoids were tested in autoimmune-prone MRL and NZB mice, the enhancing action of astaxanthin on in vitro Ab production was less significant. Furthermore, carotenoids did not potentiate or augment spontaneous Ab and immunoglobulin production by spleen cells in these strains. Taken together, carotenoids without provitamin A activity may be able to augment in vitro specific Ab production to T cell-dependent Ag partly through affecting the initial stage of Ag presentation without facilitating polyclonal B-cell activation or autoantibody production.

Publication Types:

PMID: 8346076 [PubMed - indexed for MEDLINE]

Nutr Cancer. 1991;16(2):93-105.

Studies of immunomodulating actions of carotenoids. I. Effects of beta-carotene and astaxanthin on murine lymphocyte functions and cell surface marker expression in in vitro culture system.

Jyonouchi H, **Hill RJ**, **Tomita Y**, **Good RA**.

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The immunomodulating effects of carotenoids (beta-carotene and astaxanthin) on mouse lymphocytes were studied in in vitro culture system by use of assay for mitogen responses of spleen cells, thymocyte proliferation, interleukin 2 production, and antibody (Ab) production in vitro in response to sheep red blood cells. Changes of cell surface markers on spleen lymphocytes including Ia antigen (Ag), surface immunoglobulin, B220, and Thy-1 Ag were also examined. At a concentration of 10(-8) M, carotenoids did not show any significant effect on mitogen responses (phytohemagglutinin P and concanavalin A) on murine spleen cells, irrespective of the concentrations of mitogens used. Interleukin 2 production by murine spleen cells was not significantly altered by carotenoids in the culture media (10(-7) to 10(-9) M). [3H]thymidine incorporation by B6 thymocytes was somewhat enhanced in the presence of astaxanthin or beta-carotene when cultured in the concentration of 10(6)/ml. At higher concentrations of cells (5 x 10(6)/ml), such an effect was not observed. In assays of in vitro Ab production in response to sheep red blood cells, B6 spleen cells produced significantly more Ab-forming cells (plaque-forming cells, immunoglobulins M and G) in the presence of astaxanthin (greater than 10(-8) M) but not beta-carotene. Expression of Ia Ag seemed to be moderately enhanced on both Thy-1+ and Thy-1- spleen cells in the presence of astaxanthin (greater than 10(-9) M) but not beta-carotene. The expression of Thy-1 and surface immunoglobulin seemed unchanged with the treatment of these carotenoids. These results indicate that immunomodulating actions of carotenoids are not necessarily related to provitamin A activity, because astaxanthin, which does not have provitamin A activity, showed more significant effects in these bioassays and also indicate that such actions of carotenoid demonstrated in this study may be difficult to explain only by its oxygen-quenching capacity.

Publication Types:

PMID: 1796012 [PubMed - indexed for MEDLINE]

Immunity

Clin Microbiol Infect. 2002 Jul;8(7):438-41.

Effect of antioxidants on the immune response of Helicobacter pylori.

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Antioxidants are substances capable of inhibiting oxidation. In chronic diseases, inflammatory response cells produce oxygen free radicals. Oxygen free radicals cause DNA damage, and this may lead to gene modifications that might be carcinogenic. Chronic Helicobacter pylori infection causes the production of DNA-damaging free radicals. In recent years, various groups have studied the effects of antioxidants, especially on H. pylori-associated gastric cancer. In most of the studies, it has been shown that H. pylori infection does affect the level of antioxidants measured in the gastric juice, but there are also controversial results. Recent experimental studies, both in vivo and in vitro, have shown that vitamin C and astaxanthin, a carotenoid, are not only free radical scavengers but also show antimicrobial activity against H. pylori. It has been shown that astaxanthin changes the immune response to H. pylori by shifting the Th1 response towards a Th2 T-cell response. Very few experimental studies support the epidemiologic studies, and further studies are needed to describe the effect and the mechanism of antioxidants in the H. pylori immune response.

NUTRITION AND CANCER, 36(1), 59-65

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Antitumor Activity of Astaxanthin and Its Mode of Action

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Astaxanthin, a carotenoid without Vitamin A activity, may excert antitumor activity through the enhancement of immune response. Here, we determined the effects of dietary astaxanthin on timor growth and tumor immunity against transplantable methylcholanthrene-induces fibrosarcoma (Meth-A tumor) cells. These tumor cells express a tumor antigen that induces T cell-mediated immune responses in syngenic mice. BALB/c mice were fed astaxanthin (0.02%, 40 μg/kg body wt/day in a beadlet form) mixed in a chemically defined diet starting zero, one, and three weeks before subcutaneous inoculation with tumor cells (3 x 10^5 cells, 2 times the minimal tumorigenic dose). Three weeks after inoculation, tumor size and weight were determined. We also determined cytotoic T lymphocyte (CTL) activity and interferon-γ (IFN-γ) production by tumor-draining lymph node (TDLN) and spleen cells by restimulating cells with Meth-A tumor cells in culture. The astaxanthin-fed mice had significantly lower tumor size and weight than controls when supplementation was started one and three weeks before tumor inoculation. This antitumor activity was paralleled with higher CTL activity and IFN-γ production by TNLN and spleen cells in the astaxanthin-fed mice. CTL activity by TDLN cells was highest in mice fed astaxanthin for three weeks before inoculation. When the astaxanthin-supplemented diet was started at the same time as tumor inoculation, none of these parameters were altered by dietary astaxanthin-supplemented diet was started at the same time as tumor inoculation, none of these parameters were altered by dietary astaxanthin, except IFN-γ production by spleen cells. Total serum astaxanthin concentrations were approximately 1.2 μmol/l when mice were fed astaxanthin (0.02%) for four weeks and appeared to increase in correlation with the length of astaxanthin supplementation. Our results indicate that dietary astaxanthin suppressed Meth-A tumor cell growth and stimulated immunity against Meth-A tumor antigen.

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Evaluation of therapeutic effects of astaxanthin on impairments in salivary secretion.

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Abstract

The involvement of reactive oxygen species (ROS) in the pathophysiology of Sjögren's syndrome (SS), an autoimmune disorder, and irradiation-induced impairments in salivary secretion has been reported. Meanwhile, the strong antioxidant astaxanthin (Ast) has been suggested to have therapeutic effects on various diseases. In the present study, we examined the ROS scavenging capacity of Ast using a human salivary gland epithelial cell line (HSY) and investigated the effects of Ast on salivary secretion in a mouse model of irradiation-induced salivary gland dysfunction. Furthermore, we performed a clinical study of Ast in six SS patients and six normal individuals, quantifying the volume of saliva secretion and the level of oxidative stress markers in the saliva. Ast partially suppressed hydrogen peroxide-induced ROS in HSY cells. The mouse model demonstrated that the pre-administration of Ast resulted in the suppression of irradiation-induced hyposalivation. Furthermore, the administration of Ast appeared to increase salivary output in both the SS and normal groups. The level of oxidative stress marker, hexanoyl-lysine, in the saliva was reduced after Ast intake. These results suggest that Ast might act as an ROS scavenger, providing benefits to SS patients with impaired salivary secretion.

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Cancer Prevention and Tumor Reduction

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Growth-inhibitory effects of the astaxanthin-rich alga Haematococcus pluvialis in human colon cancer cells.

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The growth-inhibitory effects of the astaxanthin-rich Haematococcus pluvialis were studied in HCT-116 colon cancer cells. H. pluvialis extract (5-25mug/ml) inhibited cell growth in a dose- and time-dependent manner, by arresting cell cycle progression and by promoting apoptosis. At 25mug/ml of H. pluvialis extract, an increase of p53, p21(WAF-1/CIP-1) and p27 expression (220%, 160%, 250%, respectively) was observed, concomitantly with a decrease of cyclin D1 expression (58%) and AKT phosphorylation (21%). Moreover, the extract, at the same concentration, strongly up-regulated apoptosis by modifying the ratio of Bax/Bcl-2 and Bcl-XL, and increased the phosphorylation of p38, JNK, and ERK1/2 by 160%, 242%, 280%, respectively. Growth-inhibitory effects by H. pluvialis were also observed in HT-29, LS-174, WiDr, SW-480 cells. This study suggests that H. pluvialis may protect from colon cancer.

PMID: 19423215 [PubMed - as supplied by publisher]

Toxicology. 2008 Jun 27;248(2-3):96-103. Epub 2008 Mar 27.

Astaxanthin inhibits cytotoxic and genotoxic effects of cyclophosphamide in mice germ cells.

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Cyclophosphamide (CP), an alkylating agent used in the treatment of several cancers as well as an immunosuppressant in rheumatoid arthritis. It is used against several cancers due to its broad spectrum efficacy, but at the same time possesses unwanted risks for occupational exposure as well as therapy related toxicities to patients. The present study was aimed to investigate the protective effect of astaxanthin (AST) a red carotenoid pigment on CP induced germ cell toxicity in male mice. CP was administered intraperitoneally (i.p.) at the dose of 50, 100 and 200mg/kg body weight to mice (20-25 g) once in a week for a period of five weeks. AST was given at the dose of 25mg/kg per oral (p.o.) for five consecutive days in a week for five weeks. The animals were sacrificed one week after the last injection of CP. The protective effect of AST against CP induced male germ cell toxicity was evaluated using body weight, testes and epididymis weight, sperm count, sperm head morphology, sperm comet assay, histology of testes and TUNEL assay. AST treatment significantly improved the testes weight, sperm count and sperm head morphology as compared to only CP treated animals. The result of comet assay showed that AST treatment significantly restored the sperm DNA damage induced by CP. Further, AST treatment showed protection against CP induced testicular toxicity as evident from testes histology and TUNEL assay. The present results indicate the chemoprotective potential of AST against CP induced germ cell toxicity in mice.

Publication Types:

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Cancer Prevention

Mol Nutr Food Res. 2006 Nov;50(11):991-5.

Visualization of astaxanthin localization in HT29 human colon adenocarcinoma cells by combined confocal resonance Raman and fluorescence microspectroscopy.

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Astaxanthin, a carotenoid found in plants and seafood, exhibits antiproliferative, antioxidant and anticarcinogenic properties. We show that astaxanthin delivered with tetrahydrofuran is effectively taken up by cultured colon adenocarcinoma cells and is localized mostly in the cytoplasm as detected by confocal resonance Raman and broad-band fluorescence microspectroscopy image analysis. Cells incubated with beta-carotene at the same concentration as astaxanthin (10 microM) showed about a 50-fold lower cellular amount of beta-carotene, as detected by HPLC. No detectable Raman signal of beta-carotene was found in cells, but a weak broad-band fluorescence signal of beta-carotene was observed. beta-Carotene, like astaxanthin, was localized mostly in the cytoplasm. The heterogeneity of astaxanthin and beta-carotene cellular distribution in cells of intestinal origin suggests that the possible defense against reactive molecules by carotenoids in these cells may also be heterogeneous.

Publication Types:

- Research Support, Non-U.S. Gov't

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Bioorg Med Chem. 2006 Aug 15;14(16):5451-8. Epub 2006 May 23.

Molecular modeling of non-covalent binding of homochiral (3S,3'S)-astaxanthin to matrix metalloproteinase-13 (MMP-13).

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Inhibitors for matrix metalloproteinases (MMPs) are under investigation for the treatment of various important chronic illnesses, including cancer, arthritis, and cardiovascular disease (CVD). In particular, MMP-13 is currently being probed as a potential key target in CVD and malignant disease due to its documented effects on extracellular matrix (ECM) remodeling, important in the pathophysiology of these diseases. Within the family of related mammalian MMP enzymes, MMP-13 possesses a large hydrophobic binding pocket relative to that of other MMPs. Homochiral astaxanthin (3S,3'S-AST; 3S,3'S-dihydroxy-beta,beta-carotene-4,4'-dione), an important antioxidant and anti-inflammatory xanthophyll carotenoid, is an active metabolite of several novel soft drugs in clinical development; it is also extensively used and tested as a human nutraceutical. In the current study, the prediction of the geometry and energetics of its binding to human MMP-13 was conducted with molecular modeling. The method used was found to predict the energy of binding of known ligands of MMP-13 with great precision. Blind docking using the whole protein target was then used in order to identify the possible binding site(s) of AST. AST was predicted to bind at several sites in close proximity to the active center. Subsequent analyses focused on the binding site at the atomic (i.e., amino acid sequence) level suggested that AST can bind to MMP-13 with high affinity and favorable energetics. Therefore, the modeling study predicts potential direct enzyme-inhibitory activity of AST against MMP-13, a behavior that may be exploited in mammalian systems in which pathological upregulation of MMP activity is paramount.

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Int J Mol Med. 2005 Nov;16(5):931-6.

Antiproliferation and induction of cell death of Phaffia rhodozyma (Xanthophyllomyces dendrorhous) extract fermented by brewer malt waste on breast cancer cells.

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Astaxanthin has been shown to have antiproliferative activity on breast cancer and skin cancer cells. However, the high cost of production, isolation and purification of purified astaxanthin from natural sources or chemically synthetic methods limit its usage on cancer therapy. We show that astaxanthin could be produced by fermentating the Phaffia rhodozyma (Xanthophyllomyces dendrorhous) yeast cells with brewer malt waste using a 20 L B. Braun fermentor. The percentage composition of astaxanthin from the P. rhodozyma was >70% of total pigment as estimated by the high performance liquid chromatographic analysis. Furthermore, the antiproliferative activity of this P. rhodozyma cell extract (PRE) was demonstrated on breast cancer cell lines including the MCF-7 (estrogen receptor positive) and MDA-MB231 (estrogen receptor negative) by using the [3-(4,5-dimethylthiazol-2-yl)-5-(3-arboxymethoxyphenyl)-2- (4-sulfophenyl)-2H-tetrazolium] (MTS) assay. No apoptotic cell death, but growth inhibitory effect was induced after 48 h of PRE incubation as suggested by morphological investigation. Anchorage-dependent clonogenicity assay showed that PRE could reduce the colony formation potential of both breast cancer cell lines. Cell death was observed from both breast cancer cell lines after incubation with PRE for 6 days. Taken together, our results showed that by using an economic method of brewer malt waste fermentation, we obtained P. rhodozyma with a high yield of astaxanthin and the corresponding PRE could have short-term growth inhibition and long-term cell death activity on breast cancer cells.

Publication Types:

PMID: 16211266 [PubMed - indexed for MEDLINE]

Cancer Prevention

Biochim Biophys Acta. 2005 May 30;1740(2):170-8. Epub 2005 Jan 25.

Cancer prevention by retinoids and carotenoids: independent action on a common target.

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Virtually all human tumors are deficient in gap junctional communication (GJC) and the restoration of GJC by forced expression of connexins reduces indices of neoplasia. The expression of connexin 43 (Cx43) is upregulated by cancer-preventive retinoids and carotenoids which correlates with the suppression of carcinogen-induced transformation in 10T1/2 cells. However, the molecular mechanism for upregulated expression is poorly understood. The retinoic acid receptor antagonist, Ro 41-5253, suppressed retinoid-induced Cx43 protein expression in 10T1/2 cells and the induction of a Cx43 luciferase reporter construct in F9 cells, but did not suppress protein expression or reporter activity induced by the non-pro-vitamin A carotenoid astaxanthin. In contrast, Cx43 induction by astaxanthin, but not by a RAR-specific retinoid, was inhibited by GW9662, a PPAR-gamma antagonist. Neither compound required protein synthesis for the induction of Cx43 mRNA, nor was the 5.0 h half-life of Cx43 mRNA altered, indicating direct transcriptional activation. The responsive region was found within -158 bp and +209 bp of the transcription start site. Site directed mutagenesis of a GC-box in this region increased basal levels of transcription and loss of retinoid responsiveness. Simultaneous treatment with a retinoid and beta-carotene or astaxanthin resulted in supra-additive Cx43 expression, again indicating separate mechanisms of gene regulation.

Publication Types:

PMID: 15949684 [PubMed - indexed for MEDLINE]

Carcinogenesis. 2005 Sep;26(9):1634-41. Epub 2005 May 11.

Inhibition of chemically-induced neoplastic transformation by a novel tetrasodium diphosphate astaxanthin derivative.

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Carotenoids have been implicated in numerous epidemiological studies as being protective against cancer at many sites, and their chemopreventive properties have been confirmed in laboratory studies. Astaxanthin (AST), primarily a carotenoid of marine origin, responsible for the pink coloration of salmon, shrimp and lobster, has received relatively little attention. As with other carotenoids, its highly lipophilic properties complicate delivery to model systems. To overcome this issue we have synthesized a novel tetrasodium diphosphate astaxanthin (pAST) derivative with aqueous dispersibility of 25.21 mg/ml. pAST was delivered to C3H/10T1/2 cells in an aqueous/ethanol solution and compared with non-esterified AST dissolved in tetrahydrofuran. We show pAST to (i) upregulate connexin 43 (Cx43) protein expression; (ii) increase the formation of Cx43 immunoreactive plaques; (iii) upregulate gap junctional intercellular communication (GJIC); and (iv) cause 100% inhibition of methylcholanthrene-induced neoplastic transformation at 10(-6) M. In all these assays, pAST was superior to non-esterified AST itself; in fact, pAST exceeded the potency of all other previously tested carotenoids in this model system. Cleavage of pAST to non-esterified (free) AST and uptake into cells was also verified by HPLC; however, levels of free AST were approximately 100-fold lower than in cells treated with AST itself, suggesting that pAST possesses intrinsic activity. The dual properties of water dispersibility (enabling parenteral administration in vivo) and increased potency should prove extremely useful in the future development of cancer chemopreventive agents.

PMID: 15888493 [PubMed - indexed for MEDLINE]

Cancer Lett. 2004 Jul 28;211(1):25-37.

Upregulation of connexin 43 protein expression and increased gap junctional communication by water soluble disodium disuccinate astaxanthin derivatives.

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Carotenoids are plant pigments whose consumption is associated with lower cancer rates in humans. Studies in experimental animal and cell systems have confirmed the cancer chemopreventive activity of these compounds. However, their extremely hydrophobic nature makes these compounds biologically unavailable unless delivered in organic solution to model systems. We have synthesized novel disodium salt disuccinate astaxanthin derivatives that possess high aqueous dispersibility. When delivered to mouse embryonic fibroblast C3H/10T1/2 cell cultures, either in aqueous or aqueous/ethanol solutions, these derivatives are biologically active. Biological activity was demonstrated by (1) upregulated expression of connexin 43 (Cx43) protein; (2) increased formation of Cx43 immunoreactive plaques in regions of the plasma membrane consistent with localization of gap junctions; (3) significantly upregulated gap junctional intercellular communication (GJIC) as demonstrated by Lucifer Yellow dye transfer after microinjection ($P < 0.03$; Fisher's Exact test). Enhanced expression of Cx43 and increased GJIC have been previously demonstrated to result in inhibition of in vitro neoplastic transformation of 10T1/2 cells as well as growth reduction of human tumors in xenografts. These novel derivatives possess increased utility as water soluble and water dispersible agents, allowing for aqueous delivery both in vitro and in vivo, properties that could enhance their potential clinical utility as potent cancer chemopreventive agents.

PMID: 15194214 [PubMed - indexed for MEDLINE]

Life Sci. 2002 Apr 21;70(21):2509-20.

Contribution of the antioxidative property of astaxanthin to its protective effect on the promotion of cancer metastasis in mice treated with restraint stress.

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We investigated the effects of astaxanthin on the antitumor effector activity of natural killer (NK) cells suppressed by stress in mice in order to define the immunological significance of astaxanthin (ASX) when combined with restraint stress treatment. When the mice were treated with restraint stress alone, the total number of spleen cells, and the level NK cell activity per spleen were reduced to a nadir on day 3. The stress also caused a significant increase in the lipid peroxidation of liver tissue. ASX (100 mg/kg/day, p.o., 4 days) improved the immunological dysfunction induced by restraint stress. On the other hand, metastatic nodules were observed in the livers of syngenic DBA/2 mice on day 12 after inoculation of P815 mastocytoma cells. Hepatic metastasis was promoted further by restraint stress when applied on day 3 before the inoculation of P815. Daily oral administration of ASX (1 mg/kg/day, p.o., 14 days) markedly attenuated the promotion of hepatic metastasis induced by restraint stress. These results suggested that astaxanthin improves antitumor immune responses by inhibiting of lipid peroxidation induced by stress.

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Cancer Prevention

Nutr Cancer. 2000;36(1):59-65.

Antitumor activity of astaxanthin and its mode of action.

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Astaxanthin, a carotenoid without vitamin A activity, may exert antitumor activity through the enhancement of immune responses. Here, we determined the effects of dietary astaxanthin on tumor growth and tumor immunity against transplantable methylcholanthrene-induced fibrosarcoma (Meth-A tumor) cells. These tumor cells express a tumor antigen that induces T cell-mediated immune responses in syngenic mice. BALB/c mice were fed astaxanthin (0.02%, 40 micrograms/kg body wt/day in a beadlet form) mixed in a chemically defined diet starting zero, one, and three weeks before subcutaneous inoculation with tumor cells (3 x 10(5) cells, 2 times the minimal tumorigenic dose). Three weeks after inoculation, tumor size and weight were determined. We also determined cytotoxic T lymphocyte (CTL) activity and interferon-gamma (IFN-gamma) production by tumor-draining lymph node (TDLN) and spleen cells by restimulating cells with Meth-A tumor cells in culture. The astaxanthin-fed mice had significantly lower tumor size and weight than controls when supplementation was started one and three weeks before tumor inoculation. This antitumor activity was paralleled with higher CTL activity and IFN-gamma production by TDLN and spleen cells in the astaxanthin-fed mice. CTL activity by TDLN cells was highest in mice fed astaxanthin for three weeks before inoculation. When the astaxanthin-supplemented diet was started at the same time as tumor inoculation, none of these parameters were altered by dietary astaxanthin, except IFN-gamma production by spleen cells. Total serum astaxanthin concentrations were approximately 1.2 mumol/l when mice were fed astaxanthin (0.02%) for four weeks and appeared to increase in correlation with the length of astaxanthin supplementation. Our results indicate that dietary astaxanthin suppressed Meth-A tumor cell growth and stimulated immunity against Meth-A tumor antigen.

Publication Types:

PMID: 10798217 [PubMed - indexed for MEDLINE]

Cancer Prevention

Cancer Lett. 2000 Apr 3;151(1):111-5.

Inhibitory effects of carotenoids on the invasion of rat ascites hepatoma cells in culture.

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The effects of carotenoids--alpha-carotene, beta-carotene, lycopene, beta-cryptoxanthin, zeaxanthin, lutein, canthaxanthin, astaxanthin--on the invasion of rat ascites hepatoma AH109A cells were investigated by co-culturing the hepatoma cells with rat mesentery-derived mesothelial cells (M-cells). All the carotenoids examined inhibited AH109A invasion in a dose-dependent manner up to 5 microM. Cancer cells previously cultured with hypoxanthine (HX) and xanthine oxidase (XO) showed a highly invasive activity. Carotenoids, 5 microM of beta-carotene and astaxanthin, suppressed this reactive oxygen species-potentiated invasive capacity by simultaneously treating AH109A cells with the carotenoids, HX and XO. These results suggest that the antioxidative property of these carotenoids may be involved in their anti-invasive action.

Publication Types:

PMID: 10766430 [PubMed - indexed for MEDLINE]

Cancer Prevention

Anticancer Res. 1999 Nov-Dec;19(6B):5223-7.

Dietary beta-carotene and astaxanthin but not canthaxanthin stimulate splenocyte function in mice.

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The in vivo modulatory effect of beta-carotene, astaxanthin and canthaxanthin on lymphocyte function was investigated. Female BALB/c mice (8 wk old) were fed a basal diet containing 0, 0.1% or 0.4% beta-carotene, astaxanthin or canthaxanthin for 0, 2 or 4 wk (n = 8/diet/period). Splenic lymphocytes were isolated and mitogen-stimulated proliferation, IL-2 production and lymphocyte cytotoxicity were assessed. Body weight and feed intake were not different among dietary treatments. Plasma carotenoids were undetectable in unsupplemented mice but concentrations of the respective carotenoids were elevated in mice fed 0.1 or 0.4% beta-carotene (0.22 and 0.39 mumol/L), astaxanthin (16.4 and 50.2 mumol/L) and canthaxanthin (5.00 and 7.02 mumol/L) respectively. Mice fed both dietary levels of beta-carotene and astaxanthin had enhanced phytohemagglutinin-induced lymphoblastogenesis compared to unsupplemented mice ($P < 0.03$). No treatment difference was detected with concanavalin A- or lipopolysaccharide-induced lympho-proliferation nor with IL-2 production ($P < 0.05$). Astaxanthin (0.1%) also enhanced lymphocyte cytotoxic activity ($P < 0.08$). In contrast, canthaxanthin did not significantly influence any of the lymphocyte functions measured. Results indicate that beta-carotene and astaxanthin but not canthaxanthin exert enhanced splenic lymphocyte function in mice.

Publication Types:

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Cancer Prevention

Anticancer Res. 1999 May-Jun;19(3A):1849-53.

A comparison of the anticancer activities of dietary beta-carotene, canthaxanthin and astaxanthin in mice in vivo.

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The anticancer activities of beta-carotene, astaxanthin and canthaxanthin against the growth of mammary tumors were studied in female eight-wk-old BALB/c mice. The mice were fed a synthetic diet containing 0, 0.1 or 0.4% beta-carotene, astaxanthin or canthaxanthin. After 3 weeks, all mice were inoculated with 1 x 10(6) WAZ-2T tumor cells into the mammary fat pad. All animals were killed on 45 d after inoculation with the tumor cells. No carotenoids were detectable in the plasma or tumor tissues of unsupplemented mice. Concentrations of plasma astaxanthin (20 to 28 mumol/L) were greater ($P < 0.05$) than that of beta-carotene (0.1 to 0.2 mumol/L) and canthaxanthin (3 to 6 mmol/L). However, in tumor tissues, the concentration of canthaxanthin (4.9 to 6.0 nmol/g) was higher than that of beta-carotene (0.2 to 0.5 nmol/g) and astaxanthin (1.2 to 2.7 nmol/g). In general, all three carotenoids decreased mammary tumor volume. Mammary tumor growth inhibition by astaxanthin was dose-dependent and was higher than that of canthaxanthin and beta-carotene. Mice fed 0.4% beta-carotene or canthaxanthin did not show further increases in tumor growth inhibition compared to those fed 0.1% of each carotenoid. Lipid peroxidation activity in tumors was lower ($P < 0.05$) in mice fed 0.4% astaxanthin, but not in those fed beta-carotene and canthaxanthin. Therefore, beta-carotene, canthaxanthin and especially astaxanthin inhibit the growth of mammary tumors in mice; their anti-tumor activity is also influenced by the supplemental dose.

Publication Types:

PMID: 10470126 [PubMed - indexed for MEDLINE]

Cancer Prevention

Br J Nutr. 1999 Mar;81(3):235-42.

Effect of dietary supplementation with carotenoids on xenobiotic metabolizing enzymes in the liver, lung, kidney and small intestine of the rat.

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The effect of 16 d intake of 300 mg carotenoids/kg diet (beta-carotene (beta C), bixin (BX), lycopene (LY), lutein (LU), canthaxanthin (CX) or astaxanthin (AX) on xenobiotic metabolizing enzymes in the liver, lung, kidney and small intestine of male Wistar rats was assessed. A control group received the basal diet (AIN-76) without carotenoids and a positive control group for enzyme induction received 3-methylcholanthrene (3-MC) at 666 mg/kg diet. Cytochrome P450 activity was assessed using the substrates ethoxyresorufin for P450 1A1, methoxyresorufin for P450 1A2, pentoxyresorufin for P450 2B1/2 and benzyloxyresorufin for P450 types 1A1/2, 2B1/2 and 3A. Glutathione-S-transferase (EC 2.5.1.18) and reduced glutathione status were assessed. Carotenoid uptake by the tissues was also determined. 3-MC and the carotenoids BX, CX and AX led to significant increases compared with control in liver, lung and kidney ethoxyresorufin-O-deethylation. Methoxyresorufin-O-demethylation activity was significantly increased in liver and lung by BX, CX and AX but only CX and AX significantly increased activity in kidney. Pentoxyresorufin-O-depentylation and benzyloxyresorufin-O-dearylation increased in liver of 3-MC-, BX-, CX- and AX-treated rats, but to a much lesser degree than for the other two substrates. Benzyloxyresorufin-O-dearylation in lung was significantly decreased by all carotenoids. Activities of any of the measured enzymes in the small intestine were undetectable in all treatment groups except the 3-MC group. Glutathione status was unaffected by any of the treatments. This is the first study identifying the carotenoids BX, CX and AX as inducers of rat lung and kidney xenobiotic metabolizing enzymes.

Publication Types:

PMID: 10434850 [PubMed - indexed for MEDLINE]

Carcinogenesis. 1998 Mar;19(3):403-11.

Dietary carotenoids inhibit aflatoxin B1-induced liver preneoplastic foci and DNA damage in the rat: role of the modulation of aflatoxin B1 metabolism.

Gradelet S, **Le Bon AM**, **Bergès R**, **Suschetet M**, **Astorg P**.

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To study the effects of carotenoids on the initiation of liver carcinogenesis by aflatoxin B1 (AFB1), male weanling rats were fed beta-carotene, beta-apo-8'-carotenal, canthaxanthin, astaxanthin or lycopene (300 mg/kg diet), or an excess of vitamin A (21000 RE/kg diet), or were injected i.p. with 3-methylcholanthrene (3-MC) (6 x 20 mg/kg body wt) before and during i.p. treatment with AFB1 (2 x 1 mg/kg body wt). The rats were later submitted to 2-acetylaminofluorene treatment and partial hepatectomy, and placental glutathione S-transferase-positive liver foci were detected and quantified. The in vivo effects of carotenoids or of 3-MC on AFB1-induced liver DNA damage were evaluated using different endpoints: liver DNA single-strand breaks (SSB) induced by AFB1, and in vivo binding of [3H]AFB1 to liver DNA and plasma albumin. Finally, the modulation of AFB1 metabolism by carotenoids or by 3-MC was investigated in vitro by incubating [14C]AFB1 with liver microsomes from rats that had been fed with carotenoids or treated by 3-MC, and the metabolites formed by HPLC were analyzed. In contrast to lycopene or to an excess of vitamin A, both of which had no effect, beta-carotene, beta-apo-8'carotenal, astaxanthin and canthaxanthin, as well as 3-MC, were very efficient in reducing the number and the size of liver preneoplastic foci. In a similar way as 3-MC, the P4501A-inducer carotenoids, beta-apo-8'-carotenal astaxanthin and canthaxanthin, decreased in vivo AFB1-induced DNA SSB and the binding of AFB1 to liver DNA and plasma albumin, and increased in vitro AFB1 metabolism to aflatoxin M1, a less genotoxic metabolite. It is concluded that these carotenoids exert their protective effect through the deviation of AFB1 metabolism towards detoxication pathways. In contrast, beta-carotene did not protect hepatic DNA from AFB1-induced alterations, and caused only minor changes of AFB1 metabolism: seemingly, its protective effect against the initiation of liver preneoplastic foci by AFB1 is mediated by other mechanisms.

Publication Types:

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Cancer Prevention

Cancer Lett. 1997 Mar 19;114(1-2):221-3.

Modulation of aflatoxin B1 carcinogenicity, genotoxicity and metabolism in rat liver by dietary carotenoids: evidence for a protective effect of CYP1A inducers.

Gradelet S, **Astorg P**, **Le Bon AM**, **Bergès R**, **Suschetet M**.

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The effects of several carotenoids of vitamin A and of 3-methylcholanthrene have been tested on the initiation of hepatocarcinogenesis by aflatoxin B1, using the sequential protocol of Solt and Farber. AFB1-induced DNA single-strand breaks and AFB1-metabolism were also assessed. The P4501A inducer carotenoids (canthaxanthin, astaxanthin, beta-apo-8'-carotenal) and 3-methylcholanthrene reduce the carcinogenicity of AFB1, divert AFB1-metabolism into the less genotoxic aflatoxin M1 and reduce AFB1-induced DNA single-strand breaks: we conclude that these carotenoids exert their protective effect through the deviation of AFB1 metabolism towards detoxification pathways. beta-Carotene decreased AFB1 carcinogenicity but did not alter its metabolism, probably acting by other mechanisms.

Publication Types:

PMID: 9103297 [PubMed - indexed for MEDLINE]

J Cell Biochem Suppl. 1997;27:35-41.

Chemoprevention by naturally occurring and synthetic agents in oral, liver, and large bowel carcinogenesis.

Mori H, **Tanaka T**, **Sugie S**, **Yoshimi N**, **Kawamori T**, **Hirose Y**, **Ohnishi M**.

Department of Pathology, Gifu University School of Medicine, Japan.

A number of naturally occurring compounds and several related synthetic agents were confirmed to exert chemopreventive properties against carcinogenesis in the digestive organs. Phenolic compounds, widely distributed as plant constituents, possess chemopreventive activities in tongue, liver, and large bowel of rodents. Of them, a simple phenolic protocatechuic acid seems to be a promising compound. Organosulfur compounds contained in the cruciferous vegetables and known to activate detoxifying enzymes are regarded as a candidate group for cancer preventive agents. We proved a strong protective effect of S-methylmethanethiosulfonate, a constituent in these vegetables, on azoxymethane (AOM)-induced large bowel carcinogenesis. Some oxygenated carotenoids (xanthophylls) are reported to have antitumor effects. Naturally occurring xanthophylls astaxanthin and canthaxanthin have considerable preventive activities on 4-nitroquinoline-1-oxide (4-NQO)-induced tongue carcinogenesis and AOM-induced large bowel carcinogenesis. A novel synthesized retinoidal butenolide, KYN-54, which suppresses large bowel as well as tongue carcinogenesis could be a useful agent for prevention of digestive organ cancers. Some trace elements are known to have anticarcinogenic effects. Magnesium hydroxide, a protective agent in colorectal carcinogenesis, inhibits c-myc expression and ornithine decarboxylase activity in the mucosal epithelium of the intestine. Our results show that many agents with preventive effects in tongue, liver, and large bowel control carcinogen-induced hyperproliferation of cells in these organs. Carcinogens used to induce large bowel cancers also induce apoptosis in the target sites. Telomerase activity is increased in the tissues of preneoplastic as well as neoplastic lesions in experimental models such as dimethylbenz[a]anthracene-induced oral carcinogenesis in hamsters. These could be useful biomarkers in studies for cancer chemoprevention.

Publication Types:

PMID: 9591191 [PubMed - indexed for MEDLINE]

Carcinogenesis. 1995 Dec;16(12):2957-63.

Suppression of azoxymethane-induced rat colon carcinogenesis by dietary administration of naturally occurring xanthophylls astaxanthin and canthaxanthin during the postinitiation phase.

Tanaka T, **Kawamori T**, **Ohnishi M**, **Makita H**, **Mori H**, **Satoh K**, **Hara A**.

First Department of Pathology, Gifu University School of Medicine, Japan.

The modulating effects of dietary feeding of two xanthophylls, astaxanthin (AX) and canthaxanthin (CX) during the postinitiation phase on colon carcinogenesis initiated with azoxymethane (AOM) were investigated in male F344 rats. Animals were initiated with AOM by weekly s.c. injections of 15 mg/kg body wt for 3 weeks and then they were fed the diets containing AX or CX at concentrations of 100 and 500 p.p.m. for 34 weeks. The others contained the groups of rats treated with AX or CX alone and untreated. At the end of the study (week 37), the incidence and multiplicity of neoplasms (adenoma and adenocarcinoma) in the large intestine of rats initiated with AOM and followed by AX or CX containing diet at a high dose (500 p.p.m.) were significantly smaller than those of rats given AOM alone ($P < 0.001$). In addition, AX or CX feeding significantly inhibited the development of aberrant crypt foci induced by AOM. Dietary exposure to AX or CX also decreased cell proliferation activity as revealed by measuring 5'-bromodeoxyuridine-labeling index as crypt cells, colonic mucosal ornithine decarboxylase activity and blood polyamine levels. These results indicate that AX and CX are possible chemopreventers for carcinogenesis of colon in addition to urinary bladder and oral cavity and such effects may be partly due to suppression of cell proliferation.

Publication Types:

PMID: 8603470 [PubMed - indexed for MEDLINE]

Cancer Res. 1995 Sep 15;55(18):4059-64.

Chemoprevention of rat oral carcinogenesis by naturally occurring xanthophylls, astaxanthin and canthaxanthin.

Tanaka T, **Makita H**, **Ohnishi M**, **Mori H**, **Satoh K**, **Hara A**.

First Department of Pathology, Gifu University School of Medicine, Japan.

The chemopreventive effects of two xanthophylls, astaxanthin (AX) and canthaxanthin (CX) on oral carcinogenesis induced by 4-nitroquinoline 1-oxide (4-NQO) was investigated in male F344 rats. Rats were given 20 ppm of 4-NQO in their drinking water for 8 weeks to induce oral neoplasms or preneoplasms. Animals were fed diets containing 100 ppm AX or CX during the initiation or postinitiation phase of 4-NQO-induced oral carcinogenesis. The others contained the groups of rats treated with AX or CX alone and untreated. At the end of the study (week 32), the incidences of preneoplastic lesions and neoplasms in the oral cavity of rats treated with 4-NQO and AX or CX were significantly smaller than those of rats given 4-NQO alone ($P < 0.001$). In particular, no oral neoplasms developed in rats fed AX and CX during the 4-NQO exposure and in those given CX after the 4-NQO administration. Similarly, the incidences of oral preneoplastic lesions (hyperplasia and dysplasia) in rats treated with 4-NQO and AX or CX were significantly smaller than that of the 4-NQO-alone group ($P < 0.05$). In addition to such tumor inhibitory potential, dietary exposure of AX or CX decreased cell proliferation activity in the nonlesional squamous epithelium exposed to 4-NQO as revealed by measuring the silver-stained nucleolar organizer regions protein number/nucleus and 5'-bromodeoxyuridine-labeling index. Also, dietary AX and CX could reduce polyamine levels of oral mucosal tissues exposed to 4-NQO. These results indicate that AX and CX are possible chemopreventers for oral carcinogenesis, and such effects may be partly due to suppression of cell proliferation.

Publication Types:

PMID: 7664280 [PubMed - indexed for MEDLINE]

Carcinogenesis. 1994 Jan;15(1):15-9.

Chemoprevention of mouse urinary bladder carcinogenesis by the naturally occurring carotenoid astaxanthin.

Tanaka T, **Morishita Y**, **Suzui M**, **Kojima T**, **Okumura A**, **Mori H**.

First Department of Pathology, Gifu University School of Medicine, Japan.

The chemopreventive effects of two xanthophylls, astaxanthin (AX) and canthaxanthin (CX), on urinary bladder carcinogenesis induced by N-butyl-N(4-hydroxybutyl)nitrosamine (OH-BBN) was investigated in male ICR mice. Mice were given 250 p.p.m. OH-BBN in drinking water for 20 weeks and after a 1 week interval with tap water, water containing AX or CX at a concentration of 50 p.p.m. was administered during subsequent 20 weeks. Other groups of mice were treated with AX or CX alone or untreated. At the end of the study (week 41), the incidences of preneoplastic lesions and neoplasms in the bladder of mice treated with OH-BBN and AX or CX were smaller than those of mice given OH-BBN. In particular, AX administration after OH-BBN exposure significantly reduced the incidence of bladder cancer (transitional cell carcinoma) ($P < 0.003$). However, the inhibition of the frequencies of such lesions in mice treated with OH-BBN and CX was not significant. Treatment with AX or CX also decreased the number/nucleus of silver-stained nucleolar organizer region proteins (AgNORs), a new index of cell proliferation, in the transitional epithelium exposed to OH-BBN. Preneoplasms and neoplasms induced by OH-BBN, and the antiproliferative potential, was greater for AX than CX. These results indicate that AX is a possible chemopreventive agent for bladder carcinogenesis and such an effect of AX may be partly due to suppression of cell proliferation.

Publication Types:

PMID: 8293542 [PubMed - indexed for MEDLINE]

Cancer Prevention

Autoimmunity. 1993;16(2):95-102.

Preventive action of carotenoids on the development of lymphadenopathy and proteinuria in MRL-lpr/lpr mice.

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Department of Public Health, School of Medicine, Kurume University, Japan.

The chemopreventive action of carotenoids on proteinuria and lymphadenopathy were examined in autoimmune-prone MRL-lpr/lpr (MRL/l) mice. They were fed a synthetic full-fed diet (16-18 kcal/mouse/day) with supplementation of beta-carotene or astaxanthin (0.19 mumoles/mouse, 3 times a week), and the development of lymphadenopathy and proteinuria were examined. MRL/l mice fed a full-fed diet without the supplementation of carotenoids or those fed a calorie-restricted (CR) diet (10-11 kcal/mouse/day, 60% calorie intake of full-fed mice) were employed as controls. CR dramatically delayed the development of proteinuria and lymphadenopathy, as reported previously. Carotenoids also significantly delayed the onset of these symptoms in MRL/l mice fed a full-fed diet. Carotenoids were half as effective as CR and astaxanthin, a carotenoid without provitamin A activity, which appeared to exert more significant preventive actions than beta-carotene in delaying the development of these symptoms. Similar chemopreventive actions of carotenoids were also demonstrated in MRL/l mice fed a regular diet (Lab Chow). CR has been shown to augment IL-2 production and to decrease serum prolactin levels in this strain, which may be related to its dramatic preventive action of autoimmunity. However, carotenoids did not affect IL-2 production nor prolactin levels in full-fed MRL/l mice. The chemopreventive actions of carotenoids observed in autoimmune-prone MRL/l mice may be attributed to yet unknown mechanisms, apart from their provitamin A activity or oxygen-quenching activity.

Publication Types:

PMID: 8180322 [PubMed - indexed for MEDLINE]

Agricultural Chemistry & Biotechnology. 40(6): 490-494. #17. Lee, S. et al. (1997).

Inhibition of benzo(a)pyrene-induced mouse forestomach neoplasia by astaxanthin containing egg yolks

Anticarcinogenic activity of astaxanthin-containing egg yolks (designate AEY) was investigated for benzo(a)pyrene (BP)-induced mouse forestomach tumorigenesis initiating regimen. Female ICR mouse (6-7 weeks of age) were housed in polycarbonated cages (5 mice/cage; 20 mice/treatment) in a humidity-and-temperature-controlled facility and permitted free access to water and food. One week later, four and 2 days prior to p.o. treatment with BP (2 mg/0.2 ml corn oil), mice were given 0.2 ml PBS containing 50 mg AEY, 100 mg AEY, 150 mg AEY, or 150 mg CEY. Control mice were only given 0.2 ml PBS. Three days later this sequence was repeated for a total of 4 times. Beginning with the first intubation and continuing thereafter, body weight and food intake were recorded once weekly. All surviving mice were sacrificed 24 weeks after the first dose of BP. Mice treated with AEY developed only about one third as many neoplasms/animal as mice in control or CEY-treated group ($p<0.05$). Reducti on effect of tumor development by AEY was dependent upon doses applied. Tumor incidence was also reduced by AEY treatments, but significantly reduced only by 150 mg AEY treatment when compared to that by control or CEY. Food intake and body weight were not affected by AEY treatment. These results indicate that AEY inhibits tumorigenesis of mouse forestomach induced by BP.

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Cancer prevention by astaxanthin, a natural carotenoid

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Astaxanthin is a natural carotenoid. The anticarcinogenic effect of astaxanthin was shown in mouse lung and liver models. The effect of astaxanthin on cell proliferation, cell cycle progression and apoptosis was examined in the HepG2 human liver cancer cell line. Astaxanthin significantly inhibited the proliferation of liver cancer cells in a dose-dependent manner. Flow cytometric analysis demonstrated that astaxanthin restrained the cell cycle progression at G1, and induced apoptosis. Further examinations by real-time quantitative RT-PCR revealed that astaxanthin enhanced the expression of p21CIP1/WAF1, GADD153 and c-myc genes. These results suggest that astaxanthin will be a promising agent for use in chemopreventive or therapeutics against cancer.

Lee, S et al. (1998). J Kor Soc food Sci Nutr 27(1): 163-167, 1998.
Language: Korean

Inhibition of Sarcoma-180 Cell-induced Mouse Ascites Cancer by Astaxanthin-containing Egg Yolk

Sang-Ho Lee, Cherl-Woo Park, Kyung-Ah Park, Young-Choon Lee, Eui-Sung Choi, Yeong Lae Ha

Abstract
Anticarcinogenic activity of astaxanthin-containing egg yolk(designate AEY) was investigated for mouse ascites carcinogenesis induced by mouse Sarcomll-I8()(S-I80) cells. Female ICR mice (8 mice/treatment, 7~8 weeks of age, 25±1g) were injected, i.p. with S-180 cells (l x 10^7 cell/ml PBS). Two days later, each mouse was given 0.lml PBS containing AEY(10, 25 or 50μg/g body weight) or control egg yolk (CEY: 50μg/g body weight) every other day for 7 times. Control mice were only given 0.lml S-180 cells and 0.lml PBS. Mice treated with 25μg/g body weight of AEY showed 24.8 days of life, which was equivalent to 138% of control mice's life (l8.0 days). Based on dose-dependant experiment of AEY, mice treated with 10μg/g body weight showed slightly longer life (l9.4 days) relative to mice treated with control mice, and mice treated with 50μg/g body weight exhibited 21.9 days of life. Mice treated with any dose of AEY exhibited longer life than mice with CEY 50μg/g body weight. Body weight of mice treated with AEY was reduced relative to that of control mice or CEY-treated mice. These results suggest that AEY inhibits the carcinogenesis of mouse ascites induced by S-180 cells.

Pure & Appl. Chem. 71, 2273 (1999).

Cancer prevention by carotenoids

Nishino, et al,

A review with 13 refs. Various natural carotenoids have been proven to have anticarcinogenic activity. Epidemiol. investigations have shown that cancer risk is inversely related to the consumption of green and yellow vegetables and fruits. As b-carotene is present in abundance in these vegetables and fruits, it has been investigated extensively as a possible cancer preventive agent. However, various carotenoids which coexist with b-carotene in vegetables and fruits also have anticarcinogenic activity, and some of these, such as a-carotene, lutein and lycopene, show a higher potency than b-carotene in suppressing exptl. carcinogenesis. Thus, we have carried out more extensive studies on cancer preventive activities of natural carotenoids in foods. For example, we found that b-cryptoxanthin showed antitumor initiating activity, as well as antitumor promoting activity. It is of interest that not only carotenoids distributed in vegetables and fruits, but also animal carot enoids, such as astaxanthin, are promising as cancer preventive agents. In the present study, the cancer preventive potential of phytoene was also confirmed. The establishment of NIH3T3 cells that produce phytoene by introducing the crtB gene provides evidence that resistance against transformation, imposed by transfection of activated H-ras oncogene, was acquired by phytoene prodn. Anal. of the action mechanism of these natural carotenoids is now in progress, and some interesting results have already been obtained; for example, various carotenoids were suggested to stimulate the expression of RB gene, an antioncogene.

Phytopharmaceuticals in Cancer Chemoprevention CRC press D Bagchi and H. Preuss Ed. 2005.

Astaxanthin and Cancer Chemoprevention

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Introduction
There are clear links between human cancers and diet.1,2 By some estimates, dietary risk
factors rank higher than tobacco usage and much higher than pollution or occupational hazards in their association with cancer deaths.3 In addition to avoidance of tobacco smoke and carcinogenic food items, regular intake of chemopreventive compounds is a promising approach for reducing cancer incidence.3,4 A number of substances naturally occurring in foodstuffs, particularly antioxidant compounds in plant products, have shown promise as potential chemopreventive agents.3-6 Among these phytonutrients, the yellow, orange and red carotenoid pigments have recently sparked much interest. In epidemiological studies, vegetable and fruit consumption has consistently been associated with reduced incidence of various cancers, 5-7 and dietary carotenoid intake from these sources has similarly been correlated with reduced cancer risk.8-10 However, several recent large-scale intervention trials failed to find any chemopreventive effect of long-term supplementation with β-carotene, the most abundant dietary carotenoid.11-13 Several naturally occurring carotenoids other than β-carotene have exhibited anticancer activity,14-17 and are being considered further as potential chemopreventive agents. Among these carotenoids, the red pigment astaxanthin is of particular interest in health
management due to its unique structural and chemical properties.18-20 This chapter will review the evidence for anticarcinogenic behavior of selected carotenoids, with an emphasis on the chemopreventive activities of astaxanthin.

J Herb Pharmacother. 2005;5(1):17-26.

A preliminary investigation of the enzymatic inhibition of 5alpha-reduction and growth of prostatic carcinoma cell line LNCap-FGC by natural astaxanthin and Saw Palmetto lipid extract in vitro.

Anderson ML.

Inhibition of 5alpha-reductase has been reported to decrease the symptoms of benign prostate hyperplasia (BPH) and possibly inhibit or help treat prostate cancer. Saw Palmetto berry lipid extract (SPLE) is reported to inhibit 5alpha-reductase and decrease the clinical symptoms of BPH. Epidemiologic studies report that carotenoids such as lycopene may inhibit prostate cancer. In this investigation the effect of the carotenoid astaxanthin, and SPLE were examined for their effect on 5alpha-reductase inhibition as well as the growth of prostatic carcinoma cells in vitro. The results show astaxanthin demonstrated 98% inhibition of 5alpha-reductase at 300 microg/mL in vitro. Alphastat, the combination of astaxanthin and SPLE, showed a 20% greater inhibition of 5alpha-reductase than SPLE alone n vitro. CONCLUSIONS: Low levels of carotenoid astaxanthin inhibit 5alpha-reductase and decrease the growth of human prostatic cancer cells in vitro. Astaxanthin added to SPLE shows greater inhibition of 5alpha-reductase than SPLE alone in vitro.

Invest New Drugs. 2009 Oct 30. [Epub ahead of print]

Astaxanthin inhibits tumor invasion by decreasing extracellular matrix production and induces apoptosis in experimental rat colon carcinogenesis by modulating the expressions of ERK-2, NFkB and COX-2.

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Abstract

Colon cancer is the third most malignant neoplasm in the world and it remains an important cause of mortality in Asian and Western countries. Astaxanthin (AST), a major component of carotenoids possesses attractive remedial features. The purpose of this study is to investigate the possible mechanism of action of astaxanthin against 1, 2 dimethyl hydrazine (DMH)-induced rat colon carcinogenesis. Wistar male rats were randomized into five groups, group 1 were control rats, group 2 were rats that received AST (15 mg/kg body wt p.o. everyday), rats in group 3 were induced with DMH (40 mg/kg body wt, s.c.), DMH-induced rats in groups 4 and 5 were either pre or post initiated with AST, respectively as in group 2. DMH-induced rats exhibited elevated expressions of Nuclear factor kappa B-p65 (NF-kappaB-p65), Cyclooxygenase-2 (COX-2), Matrixmetallo proteinases (MMP) 2/9, Proliferating cell nuclear antigen (PCNA), and Extracellular signal-regulated kinase-2 (ERK-2) as confirmed by immunofluorescence. Further, Westernblot analysis of MMPs-2/9, ERK-2 and Protein kinase B (Akt) revealed increased expressions of these proteins in DMH-induced groups of rats. AST-treatment decreased the expressions of all these vital proteins, involved in colon carcinogenesis. The ability of AST to induce apoptosis in the colon of DMH-induced rats was confirmed by Annexin-V/PI staining in a confocal microscopy, DNA fragmentation analysis and expression of caspase-3 by Western blotting. In conclusion, astaxanthin exhibits anti-inflammatory and anti-cancer effects by inducing apoptosis in DMH-induced rat colon carcinogenesis by modulating the expressions of NFkB, COX-2, MMPs-2/9, Akt and ERK-2.

PMID: 19876598 [PubMed - as supplied by publisher]

Cancer Prevention

Chem Biol Interact. 2009 Aug 14;180(3):398-406. Epub 2009 Apr 2.

Intervention of astaxanthin against cyclophosphamide-induced oxidative stress and DNA damage: a study in mice.

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Abstract

Astaxanthin, a natural and nutritional red carotenoid pigment, is used as a dietary supplement. The intention of the present study was to investigate the beneficial effects of dietary pigment astaxanthin, against cyclophosphamide-induced oxidative stress and DNA damage. The end points of evaluation of the study included: (a) malondialdehyde, glutathione and superoxide dismutase concentration in liver to detect oxidative stress; (b) normal and modified alkaline comet assays (the latter includes lesion-specific enzymes formamidopyrimidine-DNA glycosylase and endonuclease-III) to detect normal and oxidative stress-induced DNA damage by cyclophosphamide in the mouse bone marrow and the peripheral blood lymphocytes. In addition, micronucleus assay and chromosomal aberration test capable of detecting the DNA damage were also carried out in peripheral blood and bone marrow of mice. Cyclophosphamide (100 mg/kg intra-peritoneal) treatment led to significant increase in liver malondialdehyde and decreased the antioxidant enzymes glutathione and superoxide dismutase. Further, cyclophosphamide also significantly increased the DNA damage as observed from normal and modified comet assays as well as micronucleus and chromosomal aberration assay. Pre-treatment with astaxanthin (12.5, 25 and 50 mg/kg/day for 5 days per oral) resulted in the restoration of oxidative stress markers such as malondialdehyde, glutathione and superoxide dismutase in liver. The amelioration of oxidative stress with astaxanthin pre-treatment correlated well with the decreased DNA damage as evident from normal and modified alkaline comet assays of bone marrow cells and peripheral blood lymphocytes. Further astaxanthin pre-treatment also reduced the frequency of chromosomal breakage and micronucleus formation in the mouse bone marrow cells and peripheral blood reticulocytes. It is thus concluded that pre-treatment with astaxanthin attenuates cyclophosphamide-induced oxidative stress and subsequent DNA damage in mice and it can be used as a chemoprotective agent against the toxicity of anticancer drug cyclophosphamide.

PMID: 19539803 [PubMed - indexed for MEDLINE]

Cancer Lett. 2009 Sep 28;283(1):108-17. Epub 2009 May 6.

Growth-inhibitory effects of the astaxanthin-rich alga Haematococcus pluvialis in human colon cancer cells.

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Abstract

The growth-inhibitory effects of the astaxanthin-rich Haematococcus pluvialis were studied in HCT-116 colon cancer cells. H. pluvialis extract (5-25 microg/ml) inhibited cell growth in a dose- and time-dependent manner, by arresting cell cycle progression and by promoting apoptosis. At 25 microg/ml of H. pluvialis extract, an increase of p53, p21(WAF-1/CIP-1) and p27 expression (220%, 160%, 250%, respectively) was observed, concomitantly with a decrease of cyclin D1 expression (58%) and AKT phosphorylation (21%). Moreover, the extract, at the same concentration, strongly up-regulated apoptosis by modifying the ratio of Bax/Bcl-2 and Bcl-XL, and increased the phosphorylation of p38, JNK, and ERK1/2 by 160%, 242%, 280%, respectively. Growth-inhibitory effects by H. pluvialis were also observed in HT-29, LS-174, WiDr, SW-480 cells. This study suggests that H. pluvialis may protect from colon cancer.

PMID: 19423215 [PubMed - indexed for MEDLINE]

Fundam Clin Pharmacol. 2009 Apr;23(2):225-34.

Antioxidative and antiproliferative effects of astaxanthin during the initiation stages of 1,2-dimethyl hydrazine-induced experimental colon carcinogenesis.

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Department of Biochemistry, University of Madras, Guindy campus, Chennai - 600 025, Tamil Nadu, India.

Abstract

Colon cancer is one of the major causes of cancer mortality worldwide. Several carotenoids with antioxidant properties are reported for their chemopreventive nature. In this study, we have evaluated the chemopreventive efficacy of astaxanthin on lipid peroxidation, antioxidant status, total number of aberrant crypt foci (ACF), and cell proliferation in 1,2 dimethylhydrazine (DMH)-induced colon carcinogenesis using a rat model. DMH was induced subcutaneously at a dosage of 40 mg/kg body weight, twice a week for 2 weeks. Astaxanthin was administered before and after the DMH induction, orally at a concentration of 15 mg/kg body weight throughout the experimental period. At the end of 16 weeks, pre-treatment with astaxanthin markedly reduced the degree of histological lesions, ACF development and also lowered the number of argyrophilic nucleolar organizer regions. Our results also showed the decreased levels of colon enzymic and non-enzymic antioxidants and increased levels of lipid peroxidation marker levels in DMH-induced rats, which were significantly reversed on astaxanthin administration. In conclusion, the results of this study suggest that astaxanthin has an affirmative and beneficial effect against chemically induced colonic pre-neoplastic progression in rats induced by DMH.

PMID: 19645817 [PubMed - indexed for MEDLINE]

Anticancer Res. 2010 Jun;30(6):2171-5.

Effect of dietary astaxanthin at different stages of mammary tumor initiation in BALB/c mice.

Nakao R, Nelson OL, Park JS, Mathison BD, Thompson PA, Chew BP.

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Abstract

The effects of astaxanthin on tumor growth, cardiac function and immune response in mice were studied. Female BALB/c mice were fed a control diet (diet C) for 8 weeks, 0.005% astaxathin for 8 weeks (diet A), or diet C for weeks 1-5 followed by diet A thereafter (diet CA). Mice were injected with a mammary tumor cell line on day 7 and tumor growth was measured daily. Mice fed diet A had extended tumor latency and lower tumor volume ($p<0.05$). Interestingly, those fed diet CA showed the fastest tumor growth. Astaxanthin feeding elevated plasma astaxanthin concentrations; there was no difference in plasma astaxanthin between mice fed CA and those fed A. Mice fed diet A, but not CA, had a higher ($p<0.05$) natural killer cell subpopulation and plasma interferon-gamma concentration compared to those fed diet C. Astaxanthin delayed tumor growth and modulated immune response, but only when astaxanthin was given before tumor initiation. This suggests that an adequate blood astaxanthin status is needed to protect against tumor initiation; conversely, astaxanthin supplementation after tumor initiation may be contraindicated.

PMID: 20651366 [PubMed - indexed for MEDLINE]

Diabetes

Life Sci. 2007 Jan 16;80(6):522-9. Epub 2006 Oct 12.

Astaxanthin ameliorates features of metabolic syndrome in SHR/NDmcr-cp.

Hussein G, **Nakagawa T**, **Goto H**, **Shimada Y**, **Matsumoto K**, **Sankawa U**, **Watanabe H**.

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Glucose and lipid metabolic parameters play crucial roles in metabolic syndrome and its major feature of insulin resistance. This study was designed to investigate whether dietary astaxanthin oil (ASX-O) has potential effects on metabolic syndrome features in an SHR/NDmcr-cp (cp/cp) rat model. Oral administration of ASX (50 mg/kg/day) for 22 weeks induced a significant reduction in arterial blood pressure in SHRcp. It also significantly reduced the fasting blood glucose level, homeostasis index of insulin resistance (HOMA-IR), and improved insulin sensitivity. The results also showed an improved adiponectin level, a significant increase in high-density lipoprotein cholesterol, a significant decrease in plasma levels of triglycerides, and non-esterified fatty acids. Additionally, ASX showed significant effects on the white adipose tissue by decreasing the size of the fat cells. These results suggest that ASX ameliorates insulin resistance by mechanisms involving the increase of glucose uptake, and by modulating the level of circulating lipid metabolites and adiponectin.

Publication Types:

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J Cell Biochem. 2008 Apr 15;103(6):1925-37.

Astaxanthin protects mesangial cells from hyperglycemia-induced oxidative signaling.

Manabe E, **Handa O**, **Naito Y**, **Mizushima K**, **Akagiri S**, **Adachi S**, **Takagi T**, **Kokura S**, **Maoka T**, **Yoshikawa T**.

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Astaxanthin (ASX) is a carotenoid that has potent protective effects on diabetic nephropathy in mice model of type 2 diabetes. In this study, we investigated the protective mechanism of ASX on the progression of diabetic nephropathy using an in vitro model of hyperglycemia, focusing on mesangial cells. Normal human mesangial cells (NHMCs) were cultured in the medium containing normal (5 mM) or high (25 mM) concentrations of D-glucose. Reactive oxygen species (ROS) production, the activation of nuclear transcription factors such as nuclear factor kappa B (NFkappaB) and activator protein-1 (AP-1), and the expression/production of transforming growth factor-beta 1 (TGFbeta(1)) and monocyte chemoattractant protein-1 (MCP-1) were evaluated in the presence or absence of ASX. High glucose (HG) exposure induced significant ROS production in mitochondria of NHMCs, which resulted in the activation of transcription factors, and subsequent expression/production of cytokines that plays an important role in the mesangial expansion, an important event in the pathogenesis of diabetic nephropathy. ASX significantly suppressed HG-induced ROS production, the activation of transcription factors, and cytokine expression/production by NHMCs. In addition, ASX accumulated in the mitochondria of NHMCs and reduced the production of ROS-modified proteins in mitochondria. ASX may prevent the progression of diabetic nephropathy mainly through ROS scavenging effect in mitochondria of mesangial cells and thus is expected to be very useful for the prevention of diabetic nephropathy.

PMID: 17955498 [PubMed - indexed for MEDLINE]

Int J Vitam Nutr Res. 2008 Jul-Sep;78(4-5):175-82.

Inhibitory effect of astraxanthin combined with Flavangenol on oxidative stress biomarkers in streptozotocin-induced diabetic rats.

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In this study, the effect of dietary antioxidants, such as astaxanthin and Flavangenol, and a combination of both, in counteracting oxidative stress in streptozotocin-induced diabetes was investigated. Streptozotocin-induced diabetic rats were divided into four groups: control, astaxanthin, Flavangenol, and combined astaxanthin and Flavangenol (mix group). Each group other than the control group was fed with an astaxanthin diet (0.1 g/kg), Flavangenol diet (2.0 g/kg), or an astaxanthin (0.1 g/kg)-Flavangenol (2.0 g/kg) mixture diet, respectively. After 12 weeks of feeding, the results showed that the lipid peroxide levels of plasma and lens and the plasma triglyceride (TG) level in the mix group were significantly decreased by 44%, 20%, and 20%, respectively, compared with the control group. In the mix group, lipid peroxidation was also significantly reduced by 70% in the liver and 20% in the kidney compared with the control group. Furthermore, the level of urinary 8-hydroxy-2'-deoxyguanosine (8-OHdG) in the mix group was significantly lower, 36%, than the control group. The alpha-tocopherol concentrations in the plasma, liver, and kidney in the astaxanthin and mix groups were significantly higher, 3-9 times, than in the control group. The degree of cataract formation in the Flavangenol and mix groups tended to be lower than the control group. These results indicate that the combination of astaxanthin with Flvangenol has an improved protective effect on oxidative stress associated with streptozotocin-induced diabetes than either agent used alone. Thus, this combination may be beneficial in preventing the progression of diabetic complications.

PMID: 19326340 [PubMed - indexed for MEDLINE]

J Nutr Sci Vitaminol (Tokyo). 2008 Aug;54(4):329-34.

Effect of astaxanthin in combination with alpha-tocopherol or ascorbic acid against oxidative damage in diabetic ODS rats.

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The present study was performed to investigate the effect of astaxanthin in combination with other antioxidants against oxidative damage in streptozotocin (STZ)-induced diabetic Osteogenic Disorder Shionogi (ODS) rats. Diabetic-ODS rats were divided into five groups: control, astaxanthin, ascorbic acid, alpha-tocopherol, and tocotrienol. Each of the four experimental groups was administered a diet containing astaxanthin (0.1 g/kg), in combination with ascorbic acid (3.0 g/kg), alpha-tocopherol (0.1 g/kg), or tocotrienol (0.1 g/kg) for 20 wk. The effects of astaxanthin with other antioxidants on lipid peroxidation, urinary 8-hydroxy-2-deoxyguanosine (8-OHdG) excretion, serum creatinine (Cr) level, creatinine clearance (Ccr), and urinary protein content were assessed. The serum lipid peroxide levels and chemiluminescent (CL) intensity in the liver of the alpha-tocopherol and tocotrienol groups were significantly reduced in comparison to that of the control group. In the alpha-tocopherol group, urinary 8-OHdG excretion, serum Cr level, Ccr, urinary albumin excretion, and urinary protein concentration were significantly decreased as compared with those in the control group. Additionally, the CL intensity in the kidney of the alpha-tocopherol group was significantly lower, but that of the ascorbic acid group was significantly higher than that in the control group. These results indicate that dietary astaxanthin in combination with alpha-tocopherol has an inhibitory effect on oxidative stress. On the other hand, our study suggests that excessive ascorbic acid intake increases lipid peroxidation in diabetic rats.

PMID: 18797156 [PubMed - indexed for MEDLINE]

Int J Mol Med. 2006 Oct;18(4):685-95.

Microarray profiling of gene expression patterns in glomerular cells of astaxanthin-treated diabetic mice: a nutrigenomic approach.

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We have demonstrated that astaxanthin reduces glomerular oxidative stress as well as inhibits the increase in urinary albumin in diabetic db/db mice. The aim of the present study was to determine the gene expression patterns in the glomerular cells of the diabetic mouse kidney, and to investigate the effects of astaxanthin on the expression of these genes using a high-density DNA microarray. The diet administered to the astaxanthin-supplementation group was prepared by mixing a control powder with astaxanthin at a concentration of 0.02%. Glomerular cells were obtained from the kidneys of mice by laser capture microdissection. Preparation of cRNA and target hybridization were performed according to the Affymetrix GeneChip eukaryotic small sample target labeling assay protocol. The gene expression profile was evaluated by the mouse expression set 430A GeneChip. Array data analysis was carried out using Affymetrix GeneChip operating and Ingenuity Pathway analysis software. Comparison between diabetic db/db and non-diabetic db/m mice revealed that 779 probes (3.1%) were significantly affected, i.e. 550 probes were up-regulated, and 229 probes were down-regulated, both at levels of >/=1.5-fold in the diabetic mice. Ingenuity signal analysis of 550 up-regulated probes revealed the mitochondrial oxidative phosphorylation pathway as the most significantly affected caronical pathway. The affected genes were associated with complexes I, III, and IV located on the mitochondrial inner membrane, and the expression levels of these genes were decreased in mice treated with astaxanthin as compared to the levels in the control mice. In addition, the expression of many genes associated with oxidative stress, collagen synthesis, and transforming growth factor-beta signaling was enhanced in the diabetic mice, and this enhancement was slightly inhibited in the astaxanthin-treated mice. In conclusion, this genome-wide nutrigenomics approach provided insight into genes and putative genetic pathways that are thought to be affected by stimulation by high-glucose concentrations. In addition, the present approach may help us gain a better understanding of the genes and pathways involved in the anti-diabetic mechanism of astaxanthin.

Publication Types:

PMID: 16964424 [PubMed - indexed for MEDLINE]

Diabetes

Biofactors. 2004;20(1):49-59.

Prevention of diabetic nephropathy by treatment with astaxanthin in diabetic db/db mice.

Naito Y, **Uchiyama K**, **Aoi W**, **Hasegawa G**, **Nakamura N**, **Yoshida N**, **Maoka T**, **Takahashi J**, **Yoshikawa T**.

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Oxidative stress is implicated as an important mechanism by which diabetes causes nephropathy. Astaxanthin, which is found as a common pigment in algae, fish, and birds, is a carotenoid with significant potential for antioxidative activity. In this study, we examined whether chronic administration of astaxanthin could prevent the progression of diabetic nephropathy induced by oxidative stress in mice. We used female db/db mice, a rodent model of type 2 diabetes, and their non-diabetic db/m littermates. The mice were divided into three groups as follows: non-diabetic db/m, diabetic db/db, and diabetic db/db treated with astaxanthin. Blood glucose level, body weight, urinary albumin, and urinary 8-hydroxydeoxyguanosine (8-OHdG) were measured during the experiments. Histological and 8-OHdG immunohistochemical studies were performed for 12 weeks from the beginning of treatment. After 12 weeks of treatment, the astaxanthin-treated group showed a lower level of blood glucose compared with the non-treated db/db group; however, both groups had a significantly high level compared with the db/m mice. The relative mesangial area calculated by the mesangial area/total glomerular area ratio was significantly ameliorated in the astaxanthin-treated group compared with the non-treated db/db group. The increases in urinary albumin and 8-OHdG at 12 weeks of treatment were significantly inhibited by chronic treatment with astaxanthin. The 8-OHdG immunoreactive cells in glomeruli of non-treated db/db mice were more numerous than in the astaxanthin-treated db/db mice. In this study, treatment with astaxanthin ameliorated the progression and acceleration of diabetic nephropathy in the rodent model of type 2 diabetes. The results suggested that the antioxidative activity of astaxanthin reduced the oxidative stress on the kidneys and prevented renal cell damage. In conclusion, administration of astaxanthin might be a novel approach for the prevention of diabetes nephropathy.

PMID: 15096660 [PubMed - indexed for MEDLINE]

Diabetes

Redox Rep. 2002;7(5):290-3.

Astaxanthin protects beta-cells against glucose toxicity in diabetic db/db mice.

Uchiyama K, **Naito Y**, **Hasegawa G**, **Nakamura N**, **Takahashi J**, **Yoshikawa T**.

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Oxidative stress induced by hyperglycemia possibly causes the dysfunction of pancreatic beta-cells and various forms of tissue damage in patients with diabetes mellitus. Astaxanthin, a carotenoid of marine microalgae, is reported as a strong anti-oxidant inhibiting lipid peroxidation and scavenging reactive oxygen species. The aim of the present study was to examine whether astaxanthin can elicit beneficial effects on the progressive destruction of pancreatic beta-cells in db/db mice--a well-known obese model of type 2 diabetes. We used diabetic C57BL/KsJ-db/db mice and db/m for the control. Astaxanthin treatment was started at 6 weeks of age and its effects were evaluated at 10, 14, and 18 weeks of age by non-fasting blood glucose levels, intraperitoneal glucose tolerance test including insulin secretion, and beta-cell histology. The non-fasting blood glucose level in db/db mice was significantly higher than that of db/m mice, and the higher level of blood glucose in db/db mice was significantly decreased after treatment with astaxanthin. The ability of islet cells to secrete insulin, as determined by the intraperitoneal glucose tolerance test, was preserved in the astaxanthin-treated group. Histology of the pancreas revealed no significant differences in the beta-cell mass between astaxanthin-treated and -untreated db/db mice. In conclusion, these results indicate that astaxanthin can exert beneficial effects in diabetes, with preservation of beta-cell function. This finding suggests that anti-oxidants may be potentially useful for reducing glucose toxicity.

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Redox Report, Vol. 7, No. 5, 2002 290-3

Astaxanthin protects β-cells against glucose toxicity in diabetic db/db mice

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Oxidative stress induced by hyperglycemia possibly causes the dysfunction of pancreatic β–cells and various forms of tissue damage in patients with diabetes mellitus. Astaxanthin, a carotenoid of marine microalgae, is reported as a strong anti-oxidant inhibiting lipid peroxidation and scavenging reactive oxygen species. The aim of the present study was to examine whether astaxanthin can elicit beneficial effects on the progressive destruction of pancreatic -cells in db/db mice β – a well-known obese model of type 2 diabetes. We used diabetic C57BL/KsJ-db/db mice and db/m for the control. Astaxanthin treatment was started at 6 weeks of age and its effects were evaluated at 10, 14, and 18 weeks of age by non-fasting blood glucose levels, intraperitoneal glucose tolerance test including insulin secretion, and -cell histology. The non-fasting blood glucose level in db/db mice was significantly higher than that of db/m mice, and the higher level of blood glucose in db/db mice was significantly decreased after treatment with astaxanthin. The ability of islet cells to secrete insulin, as determined by the intraperitoneal glucose tolerance test, was preserved in the astaxanthin-treated group. Histology of the pancreas revealed no significant differences in the -cell mass between astaxanthin-treated and -untreated db/db mice. In conclusion, these results indicate that astaxanthin can exert beneficial effects in diabetes, with preservation of β-cell function. This finding suggests that anti-oxidants may be potentially useful for reducing glucose toxicity.

Chem Biol Interact. 2010 Aug 5;186(3):306-15. Epub 2010 May 31.

Astaxanthin ameliorates the redox imbalance in lymphocytes of experimental diabetic rats.

Otton R, Marin DP, Bolin AP, Santos Rde C, Polotow TG, Sampaio SC, de Barros MP.

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Abstract

Diabetes mellitus is a syndrome of impaired insulin secretion/sensitivity and frequently diagnosed by hyperglycemia, lipid abnormalities, and vascular complications. The diabetic 'glucolipotoxicity' also induces immunodepression in patients by redox impairment of immune cells. Astaxanthin (ASTA) is a pinkish-orange carotenoid found in many marine foods (e.g. shrimp, crabs, salmon), which has powerful antioxidant, photoprotective, antitumor, and cardioprotective properties. Aiming for an antioxidant therapy against diabetic immunodepression, we here tested the ability of prophylactic ASTA supplementation (30 days, 20 mg ASTA/kg BW) to oppose the redox impairment observed in isolated lymphocytes from alloxan-induced diabetic Wistar rats. The redox status of lymphocytes were thoroughly screened by measuring: (i) production of superoxide (O(2)(-)), nitric oxide (NO), and hydrogen peroxide (H(2)O(2)); (ii) cytosolic Ca(2+); (iii) indexes of oxidative injury; and (iv) activities of major antioxidant enzymes. Hypolipidemic and antioxidant effects of ASTA in plasma of ASTA-fed/diabetic rats were apparently reflected in the circulating lymphocytes, since lower activities of catalase, restored ratio between glutathione peroxidase and glutathione reductase activities and lower scores of lipid oxidation were concomitantly measured in those immune cells. Noteworthy, lower production of NO and O(2)(-) (precursors of peroxynitrite), and lower cytosolic Ca(2+) indicate a hypothetical antiapoptotic effect of ASTA in diabetic lymphocytes. However, questions are still open regarding the proper ASTA supplementation dose needed to balance efficient antioxidant protection and essential NO/H(2)O(2)-mediated proliferative capacities of diabetic lymphocytes.

PMID: 20513374 [PubMed - indexed for MEDLINE]

Int Endod J. 2010 Jun 8. [Epub ahead of print]

In vivo astaxanthin treatment partially prevents antioxidant alterations in dental pulp from alloxan-induced diabetic rats.

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Abstract

Leite MF, de Lima A, Massuyama MM, Otton R.In vivo astaxanthin treatment partially prevents antioxidant alterations in dental pulp from alloxan-induced diabetic rats. International Endodontic Journal. Abstract Aim To evaluate the effect of astaxanthin on antioxidant parameters of dental pulp from diabetic rats. The hypothesis tested was that supplementation of diabetic rats with astaxanthin might eliminate, or at least attenuate, the defect in their antioxidative status. Methodology Wistar rats (n = 32) were divided into four groups: untreated control, treated control, untreated diabetic and treated diabetic rats. A prophylactic dose of astaxanthin (20 mg kg(-1) body weight) was administered daily by gavage for 30 days. On day 23, diabetes was induced by injection of alloxan (60 mg kg(-1) body weight). After 7 days of diabetes induction, the rats were killed, and pulp tissue from incisor teeth removed. Superoxide dismutase (SOD), catalase, glutathione peroxidase (GPx) and reductase activities were determined. Data were compared by anova and the Newman-Keuls test ($P < 0.05$). Results Diabetes caused a reduction in SOD, GPx and reductase activity in dental pulp tissue. Astaxanthin had no effect on SOD and catalase activities; however, it stimulated GPx in control and diabetic rats. Conclusions Diabetes altered the antioxidant system in dental pulp tissue; astaxanthin partially improved the diabetic complications.

PMID: 20546046 [PubMed - as supplied by publisher]

Arch Oral Biol. 2010 Jul;55(7):479-85.

Astaxanthin restores the enzymatic antioxidant profile in salivary gland of alloxan-induced diabetic rats.

Leite MF, Lima AM, Massuyama MM, Otton R.

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Abstract

OBJECTIVE: To evaluate the effect of astaxanthin on antioxidant parameters of salivary gland from diabetic rats. The hypothesis of the study was whether the supplementation of diabetic rats with astaxanthin might antagonize, or at least prevent, the defect in their antioxidative status.

DESIGN: Wistar rats (n=32) were divided in 4 groups: untreated control, treated control, untreated diabetic and treated diabetic rats. Astaxanthin (20mg/kg body weight) was administered daily by gavage for 30 days. On day 23, diabetes was induced by injection of alloxan (60 mg/kg body weight). After 7 days of diabetes induction, the rats were killed and submandibular and parotid removed. Superoxide dismutase (SOD), catalase, glutathione peroxidase and reductase activities and the content of thiol groups were determined. Data were compared by ANOVA and the Tukey test ($p<0.05$).

RESULTS: Diabetes caused a reduction of SOD, and thiol content and increase of catalase and glutathione peroxidase activities of submandibular gland whilst in the parotid gland diabetes caused an increase of thiol content and no effect in the antioxidant system. The astaxanthin restores the enzymatic activities in the salivary gland, however does not prevent its oxidative damage.

CONCLUSION: The submandibular gland presented more susceptibility to oxidative alterations induced by diabetes. Astaxanthin presented a positive effect on the oxidative protection of the salivary gland from diabetic rats.

PMID: 20510163 [PubMed - in process]

J Agric Food Chem. 2009 Oct 14;57(19):8793-7.

Protection against oxidative stress, inflammation, and apoptosis of high-glucose-exposed proximal tubular epithelial cells by astaxanthin.

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Department of Dental Hygiene, Busan Women's College, Busanjin-Gu, Busan, Korea.

Abstract

Astaxanthin is a carotenoid with powerful antioxidant properties that exists naturally in various plants, algae, and seafood. The purpose of the present study is to examine the protective action of astaxanthin against high-glucose-induced oxidative stress, inflammation, and apoptosis in proximal tubular epithelial cells (PTECs). To assess the efficacy of astaxanthin, several key markers and activities were measured, including lipid peroxidation, total reactive species (RS), superoxide (*O(2)), nitric oxide (NO*), and peroxynitrite (ONOO(-)), as well as expressions of inflammatory proteins, inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2), nuclear factor-kappa B (NF-kappaB) nuclear translocation, and levels of Bcl2/Bax protein. Results showed that astaxanthin effectively suppressed lipid peroxidation, total RS, *O(2), NO*, ONOO(-), iNOS and COX-2 protein levels, NF-kappaB nuclear translocation, and pro-apototic Bax, whereas it increased anti-apoptotic Bcl2 protein levels. On the basis of these findings, it was concluded that in PTECs, astaxanthin has a protective efficacy against several deleterious effects caused by high glucose exposure and proposed that astaxanthin should be explored further as a potential antidiabetic remedy for the treatment of diabetic nephropathy.

PMID: 19731916 [PubMed - indexed for MEDLINE]

Ulcers and Gastrointestinal Health

Eur J Pharmacol. 2005 May 2;514(1):53-9. Epub 2005 Apr 20.

Protective effect of astaxanthin on naproxen-induced gastric antral ulceration in rats.

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Frequently used for humans as non-steroidal anti-inflammatory drug, naproxen has been known to induce ulcerative gastric lesion. The present study investigated the in vivo protective effect of astaxanthin isolated from Xanthophyllomyces dendrorhous against naproxen-induced gastric antral ulceration in rats. The oral administration of astaxanthin (1, 5, and 25 mg/kg of body weight) showed a significant protection against naproxen (80 mg/kg of body weight)-induced gastric antral ulcer and inhibited elevation of the lipid peroxide level in gastric mucosa. In addition, pretreatment of astaxanthin resulted in a significant increase in the activities of radical scavenging enzymes such as superoxide dismutase, catalase, and glutathione peroxidase. A histologic examination clearly proved that the acute gastric mucosal lesion induced by naproxen nearly disappeared after the pretreatment of astaxanthin. These results suggest that astaxanthin removes the lipid peroxides and free radicals induced by naproxen, and it may offer potential remedy of gastric ulceration.

PMID: 15878324 [PubMed - indexed for MEDLINE]

Yao Xue Xue Bao. 2009 May;44(5):558-60.

[Therapeutic effect of astaxanthin on acetic acid-induced gastric ulcer in rats]

[Article in Chinese]

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Abstract

This study is to investigate therapeutic effect of astaxanthin on acetic acid-induced gastric ulcer in rats. Rats were divided into control group, ulcer control group, and astaxanthin (5, 10, and 25 mg x kg(-1)) groups at random, 8 rats in each group. After administered for 10 days consecutively, all the rats were sacrificed. The area of ulcer and the levels of MDA, SOD, CAT and GSH-Px in gastric mucosa were measured. Compared with ulcer control group, in astaxanthin (5, 10, and 25 mg x kg(-1)) groups, the area of ulcer was decreased significantly. Level of MDA decreased while activities of SOD, CAT and GSH-Px increased ($P < 0.05$). Astaxanthin has good therapeutic effect on acetic acid-induced gastric ulcer in rats. Eliminating free radical and improving local blood circulation of the ulcer may be the mechanism of action.

PMID: 19618736 [PubMed - indexed for MEDLINE]

Eur J Pharmacol. 2008 Aug 20;590(1-3):387-95. Epub 2008 Jun 16.

Ulcer preventive and antioxidative properties of astaxanthin from Haematococcus pluvialis.

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The anti-ulcer properties of astaxanthin fractions such as total carotenoid and astaxanthin esters from Haematococcus pluvialis were evaluated in ethanol-induced gastric ulcers in rats. Since oxygen radical release is a pathogenic factor of ethanol-induced gastric damage, astaxanthin - a free radical scavenger, was investigated as a potential ulcer preventive agent. Astaxanthin fractions - total carotenoid and astaxanthin esters were orally administered to experimental rats at 100, 250 and 500 microg/kg b.w. prior to ulcer induction. Alcian blue binding assay indicates that, total carotenoid and astaxanthin esters at 500 microg/kg b.w could protect gastric mucin approximately 40% and 67% respectively. Pre-treatment with astaxanthin esters, also resulted in significant increase in antioxidant enzyme levels - catalase, superoxide dismutase, and glutathione peroxidase in stomach homogenate. Histopathological examination substantiated the protective effect of astaxanthin in pre-treated rats. The increased antioxidant potencies such as free radical scavenging activity with an IC(50) of approximately 8 microg/ml and reducing power abilities (59 x 10(3) U/g) in vitro, reveal that H. pluvialis astaxanthin may protect gastric mucosal injury by antioxidative mechanism. In addition, approximately 23 fold increased lipoxygenase-inhibitory property, in comparison with standard astaxanthin and significant H(+), K(+)-ATPase-inhibitory activity of astaxanthin esters, in comparison with known proton pump blocking anti-ulcer drug - omeprazole, may envisage the potential gastroprotective effect by regulating the gastric mucosal injury and gastric acid secretion by the gastric cell during ulcer disease.

Publication Types:

PMID: 18602387 [PubMed - indexed for MEDLINE]

Phytomedicine. 2008 Jun;15(6-7):391-9. Epub 2008 May 7.

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.

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OBJECTIVES: 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. DESIGN: The study was a controlled, prospective, randomized, and double blind trial. PARTICIPANTS: Patients with functional dyspepsia, divided into three groups with 44 individuals in each group (placebo, 16mg, or 40mg 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 (40mg) dose compared to the other treatment groups (16mg 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.

Publication Types:

PMID: 18467083 [PubMed - indexed for MEDLINE]

FEMS Immunol Med Microbiol. 2007 Jul;50(2):244-8. Epub 2007 May 23.

Gastric inflammatory markers and interleukins in patients with functional dyspepsia treated with astaxanthin.

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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. Astaxanthin had an effect on the inflammation and on the density of H. pylori in mice in a study where the diet could be standardized without antioxidants (Bennedsen et al., 1999). These dietary conditions are impossible in studies involving humans, and may be due to the minor effect when the host have access to antioxidants in their diet.

Publication Types:

PMID: 17521392 [PubMed - indexed for MEDLINE]

J Nutr Sci Vitaminol (Tokyo). 2005 Jun;51(3):135-41.

Effects of astaxanthin and vitamin C on the prevention of gastric ulcerations in stressed rats.

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Astaxanthin (Asx), one of the carotenoids, is a red pigment in fish and Crustaceans, and possesses stronger reduction properties than conventional carotenoids, like beta-carotene. However, little is known about the biochemical properties and physiological functions of astaxanthin. The effects of astaxanthin and vitamin C on stressed rats were studied physiologically and biochemically. beta-Carotene and three kinds of astaxanthins, which were extracted from Haematococcus and Phaffia, and synthesized chemically, were used in these experiments. These rats given astaxanthins or beta-carotene had stress induced on the 12th day by immersing the rats in chest-level water at 20 degrees C for 24 h after fasting for 24 h. Rats given astaxanthins or beta-carotene prior to stressing were appreciably protected against the evolution of gastric ulcerations in relation to control rats. Ulcer indexes in particular were smaller with the rat group fed astaxanthin extracted from Haematococcus than the other groups. Next, the effects of Asx and/or vitamin C on the protection of evolution of gastric ulcer in stressed rats were persued by the same methods as described above. The results showed that rats given Asx or vitamin C were appreciably protected against the evolution of gastric ulcerations in relation to control rats. The effects were more intense, especially in rats simultaneously supplied Asx and vitamin C than in rats taking either Asx or vitamin C. It was suggested that the simultaneous supplementation of food substances with astaxanthin and vitamin C would supply enough antioxidants to offset stress-related injuries.

PMID: 16161762 [PubMed - indexed for MEDLINE]

Biosci Biotechnol Biochem. 2005 Jul;69(7):1300-5.

Suppressive effect of astaxanthin isolated from the Xanthophyllomyces dendrorhous mutant on ethanol-induced gastric mucosal injury in rats.

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Ethanol has been found to induce ulcerative gastric lesion in humans. The present study investigated the in vivo protective effect of astaxanthin isolated from the Xanthophyllomyces dendrorhous mutant against ethanol-induced gastric mucosal injury in rats. The rats were treated with 80% ethanol for 3 d after pretreatment with two doses of astaxanthin (5 and 25 mg/kg of body weight respectively) for 3 d, while the control rats received only 80% ethanol for 3 d. The oral administration of astaxanthin (5 and 25 mg/kg of body weight) showed significant protection against ethanol-induced gastric lesion and inhibited elevation of the lipid peroxide level in gastric mucosa. In addition, pretreatment with astaxanthin resulted in a significant increase in the activities of radical scavenging enzymes such as superoxide dismutase, catalase, and glutathione peroxidase. A histologic examination clearly indicated that the acute gastric mucosal lesion induced by ethanol nearly disappeared after pretreatment with astaxanthin.

PMID: 16041134 [PubMed - indexed for MEDLINE]

Clin Microbiol Infect. 2002 Jul;8(7):438-41.

Effect of antioxidants on the immune response of Helicobacter pylori.

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Antioxidants are substances capable of inhibiting oxidation. In chronic diseases, inflammatory response cells produce oxygen free radicals. Oxygen free radicals cause DNA damage, and this may lead to gene modifications that might be carcinogenic. Chronic Helicobacter pylori infection causes the production of DNA-damaging free radicals. In recent years, various groups have studied the effects of antioxidants, especially on H. pylori-associated gastric cancer. In most of the studies, it has been shown that H. pylori infection does affect the level of antioxidants measured in the gastric juice, but there are also controversial results. Recent experimental studies, both in vivo and in vitro, have shown that vitamin C and astaxanthin, a carotenoid, are not only free radical scavengers but also show antimicrobial activity against H. pylori. It has been shown that astaxanthin changes the immune response to H. pylori by shifting the Th1 response towards a Th2 T-cell response. Very few experimental studies support the epidemiologic studies, and further studies are needed to describe the effect and the mechanism of antioxidants in the H. pylori immune response.

Publication Types:

PMID: 12199857 [PubMed - indexed for MEDLINE]

Antimicrob Agents Chemother. 2000 Sep;44(9):2452-7.

Astaxanthin-rich algal meal and vitamin C inhibit Helicobacter pylori infection in BALB/cA mice.

Wang X, **Willén R**, **Wadström T**.

Department of Infectious Diseases and Medical Microbiology, University of Lund, Sweden.

Helicobacter pylori infection in humans is associated with chronic type B gastritis, peptic ulcer disease, and gastric carcinoma. A high intake of carotenoids and vitamin C has been proposed to prevent development of gastric malignancies. The aim of this study was to explore if the microalga Haematococcus pluvialis rich in the carotenoid astaxanthin and vitamin C can inhibit experimental H. pylori infection in a BALB/cA mouse model. Six-week-old BALB/cA mice were infected with the mouse-passaged H. pylori strain 119/95. At 2 weeks postinoculation mice were treated orally once daily for 10 days (i) with different doses of algal meal rich in astaxanthin (0.4, 2, and 4 g/kg of body weight, with the astaxanthin content at 10, 50, and 100 mg/kg, respectively), (ii) with a control meal (algal meal without astaxanthin, 4 g/kg), or (iii) with vitamin C (400 mg/kg). Five mice from each group were sacrificed 1 day after the cessation of treatment, and the other five animals were sacrificed 10 days after the cessation of treatment. Culture of H. pylori and determination of the inflammation score of the gastric mucosae were used to determine the outcome of the treatment. Mice treated with astaxanthin-rich algal meal or vitamin C showed significantly lower colonization levels and lower inflammation scores than those of untreated or control-meal-treated animals at 1 day and 10 days after the cessation of treatment. Lipid peroxidation was significantly decreased in mice treated with the astaxanthin-rich algal meal and vitamin C compared with that of animals not treated or treated with the control meal. Both astaxanthin-rich algal meal and vitamin C showed an inhibitory effect on H. pylori growth in vitro. In conclusion, antioxidants may be a new strategy for treating H. pylori infection in humans.

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PMCID: PMC90084

Immunol Lett. 1999 Dec 1;70(3):185-9.

Treatment of H. pylori infected mice with antioxidant astaxanthin reduces gastric inflammation, bacterial load and modulates cytokine release by splenocytes.

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Helicobacter pylori is a gram-negative bacterium affecting about half of the world population, causing chronic gastritis type B dominated by activated phagocytes. In some patients the disease evolves into gastric ulcer, duodenal ulcer, gastric cancer or MALT lymphoma. The pathogenesis is in part caused by the immunological response. In mouse models and in human disease, the mucosal immune response is characterized by activated phagocytes. Mucosal T-lymphocytes are producing IFN-gamma thus increasing mucosal inflammation and mucosal damage. A low dietary intake of antioxidants such as carotenoids and vitamin C may be an important factor for acquisition of H. pylori by humans. Dietary antioxidants may also affect both acquisition of the infection and the bacterial load of H. pylori infected mice. Antioxidants, including carotenoids, have anti-inflammatory effects. The aim of the present study was to investigate whether dietary antoxidant induced modulation of H. pylori in mice affected the cytokines produced by H. pylori specific T-cells. We found that treatment of H. pylori infected mice with an algal cell extract containing the antioxidant astaxanthin reduces bacterial load and gastric inflammation. These changes are associated with a shift of the T-lymphocyte response from a predominant Th1-response dominated by IFN-gamma to a Th1/Th2-response with IFN-gamma and IL-4. To our knowledge, a switch from a Th1-response to a mixed Th1/Th2-response during an ongoing infection has not been reported previously.

Publication Types:

PMID: 10656672 [PubMed - indexed for MEDLINE]

Antimicrob Agents Chemother. 2000 Sep;44(9):2452-7

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Wang X, **Willen R**, **Wadstrom T**.

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Helicobacter pylori infection in humans is associated with chronic type B gastritis, peptic ulcer disease, and gastric carcinoma. A high intake of carotenoids and vitamin C has been proposed to prevent development of gastric malignancies. The aim of this study was to explore if the microalga Haematococcus pluvialis rich in the carotenoid astaxanthin and vitamin C can inhibit experimental H. pylori infection in a BALB/cA mouse model. Six-week-old BALB/cA mice were infected with the mouse-passaged H. pylori strain 119/95. At 2 weeks postinoculation mice were treated orally once daily for 10 days (i) with different doses of algal meal rich in astaxanthin (0.4, 2, and 4 g/kg of body weight, with the astaxanthin content at 10, 50, and 100 mg/kg, respectively), (ii) with a control meal (algal meal without astaxanthin, 4 g/kg), or (iii) with vitamin C (400 mg/kg). Five mice from each group were sacrificed 1 day after the cessation of treatment, and the other five animals were sacrificed 10 days after the cessation of treatment. Culture of H. pylori and determination of the inflammation score of the gastric mucosae were used to determine the outcome of the treatment. Mice treated with astaxanthin-rich algal meal or vitamin C showed significantly lower colonization levels and lower inflammation scores than those of untreated or control-meal-treated animals at 1 day and 10 days after the cessation of treatment. Lipid peroxidation was significantly decreased in mice treated with the astaxanthin-rich algal meal and vitamin C compared with that of animals not treated or treated with the control meal. Both astaxanthin-rich algal meal and vitamin C showed an inhibitory effect on H. pylori growth in vitro. In conclusion, antioxidants may be a new strategy for treating H. pylori infection in humans.

Applications for Athletes

Biochem Biophys Res Commun. 2008 Feb 22;366(4):892-7. Epub 2007 Dec 17.

Astaxanthin improves muscle lipid metabolism in exercise via inhibitory effect of oxidative CPT I modification.

Aoi W, **Naito Y**, **Takanami Y**, **Ishii T**, **Kawai Y**, **Akagiri S**, **Kato Y**, **Osawa T**, **Yoshikawa T**.

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Intracellular redox balance may affect nutrient metabolism in skeletal muscle. Astaxanthin, a carotenoid contained in various natural foods, exerts high antioxidative capacity in the skeletal muscles. The present study investigated the effect of astaxanthin on muscle lipid metabolism in exercise. ICR mice (8 weeks old) were divided into four different groups: sedentary, sedentary treated with astaxanthin, running exercise, and exercise treated with astaxanthin. After 4 weeks of treatment, exercise groups performed treadmill running. Astaxanthin increased fat utilization during exercise compared with mice on a normal diet with prolongation of the running time to exhaustion. Colocalization of fatty acid translocase with carnitine palmitoyltransferase I (CPT I) in skeletal muscle was increased by astaxanthin. We also found that hexanoyl-lysine modification of CPT I was increased by exercise, while astaxanthin prevented this increase. In additional experiment, we found that astaxanthin treatment accelerated the decrease of body fat accumulation with exercise training. Our results suggested that astaxanthin promoted lipid metabolism rather than glucose utilization during exercise via CPT I activation, which led to improvement of endurance and efficient reduction of adipose tissue with training.

Publication Types:

- Research Support, Non-U.S. Gov't

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Biol Pharm Bull. 2006 Oct;29(10):2106-10.

Effects of astaxanthin supplementation on exercise-induced fatigue in mice.

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Laboratory of Nutraceuticals and Functional Foods Science, Graduate School of Marine Science and Technology, Tokyo University of Marine Science and Technology, Tokyo, Japan.

The present study was designed to determine the effect of astaxanthin on endurance capacity in male mice aged 4 weeks. Mice were given orally either vehicle or astaxanthin (1.2, 6, or 30 mg/kg body weight) by stomach intubation for 5 weeks. The astaxanthin group showed a significant increase in swimming time to exhaustion as compared to the control group. Blood lactate concentration in the astaxanthin groups was significantly lower than in the control group. In the control group, plasma non-esterfied fatty acid (NEFA) and plasma glucose were decreased by swimming exercise, but in the astaxanthin group, NEFA and plasma glucose were significantly higher than in the control group. Astaxanthin treatment also significantly decreased fat accumulation. These results suggest that improvement in swimming endurance by the administration of astaxanthin is caused by an increase in utilization of fatty acids as an energy source.

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Antioxid Redox Signal. 2003 Feb;5(1):139-44.

Astaxanthin limits exercise-induced skeletal and cardiac muscle damage in mice.

Aoi W, **Naito Y**, **Sakuma K**, **Kuchide M**, **Tokuda H**, **Maoka T**, **Toyokuni S**, **Oka S**, **Yasuhara M**, **Yoshikawa T**.

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Dietary antioxidants may attenuate oxidative damage from strenuous exercise in various tissues. Beneficial effects of the antioxidant astaxanthin have been demonstrated in vitro, but not yet in vivo. We investigated the effect of dietary supplementation with astaxanthin on oxidative damage induced by strenuous exercise in mouse gastrocnemius and heart. C57BL/6 mice (7 weeks old) were divided into groups: rested control, intense exercise, and exercise with astaxanthin supplementation. After 3 weeks of exercise acclimation, both exercise groups ran on a treadmill at 28 m/min until exhaustion. Exercise-increased 4-hydroxy-2-nonenal-modified protein and 8-hydroxy-2'-deoxyguanosine in gastrocnemius and heart were blunted in the astaxanthin group. Increases in plasma creatine kinase activity, and in myeloperoxidase activity in gastrocnemius and heart, also were lessened by astaxanthin. Astaxanthin showed accumulation in gastrocnemius and heart from the 3 week supplementation. Astaxanthin can attenuate exercise-induced damage in mouse skeletal muscle and heart, including an associated neutrophil infiltration that induces further damage.

PMID: 12626126 [PubMed - indexed for MEDLINE]

Journal of Clinical Therapeutics & Medicines VOL.18;NO.9;PAGE.1085-1100(2002)

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

SAWAKI KEISUKE; YOSHIGI HIROSHI; AOKI KAZUHIRO; KOIKAWA NATSUE; 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.

Mera Pharmaceuticals, Inc. Review presented at the 1st Congress of the International Society for Applied Phycology/9th International Conference on Applied Phycology, May 2002, Almeria, Spain.

Haematococcus astaxanthin: health and nutrition applications: Exercise survey with 88% reporting improvement

Guerin, M, Huntley, M, Olaizola, M.

"In March 2001, a health survey looked at the various positive effects of Astaxanthin on exercise. The survey involved 247 between the ages of 20 and 87 years. 146 of those taking part reported problems with muscle and joint soreness. When taking Astaxanthin, 88% of participants reported improvement. In all cases, the more exercise an individual did, the more benefit was experienced."

Applications for Athletes: Muscle and Joint Soreness

PhysioL Chern. Phys. & M«l. NMR. (1990) 22:27-31:\

Inhibition of Oxidative Injury of Biological Membranes by Astaxanthin

Michi Kurashige, Eiji Okimasu, Masayasu Inoue and Kozo Utsumi

The value of astaxanthin, a carotenoid pigment, in the treatment of oxidative injury is assessed. Astaxanthin protects the mitochondria or vitamin E-deficient rats from damage by Fe2+ catalyzed lipid peroxidation both in vim and in vitro. The inhibitory effect of astaxanthin on mitochondrial lipid peroxidation is stronger than that of a-tocopherol. Thin layer chromatographic analysis shows that the change in phospholipid components of erythrocytes from vitamin E-deficient rats induced by Fe^{2}+ and Fe^{3}+ -xanthine/xanthine oxidase system was significantly suppressed by astaxanthin. Carrageenan-induces inflammation of the paw is also significantly inhibited by administration of astaxanthin. These data indicate that astaxanthin functions as a potent antioxidant both in vivo and in vitro.

J Nutr Biochem. 2009 May 6. [Epub ahead of print]

Astaxanthin protects mitochondrial redox state and functional integrity against oxidative stress.

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Mitochondria combine the production of energy with an efficient chain of reduction-oxidation (redox) reactions but also with the unavoidable production of reactive oxygen species. Oxidative stress leading to mitochondrial dysfunction is a critical factor in many diseases, such as cancer and neurodegenerative and lifestyle-related diseases. Effective antioxidants thus offer great therapeutic and preventive promise. Investigating the efficacy of antioxidants, we found that a carotenoid, astaxanthin (AX), decreased physiologically occurring oxidative stress and protected cultured cells against strong oxidative stress induced with a respiratory inhibitor. Moreover, AX improved maintenance of a high mitochondrial membrane potential and stimulated respiration. Investigating how AX stimulates and interacts with mitochondria, a redox-sensitive fluorescent protein (roGFP1) was stably expressed in the cytosol and mitochondrial matrix to measure the redox state in the respective compartments. AX at nanomolar concentrations was effective in maintaining mitochondria in a reduced state. Additionally, AX improved the ability of mitochondria to remain in a reduced state under oxidative challenge. Taken together, these results suggest that AX is effective in improving mitochondrial function through retaining mitochondria in the reduced state.

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ASTAXANTHIN SUPPLEMENTATION

A.C. Fry, B.K. Schilling, L.Z.F. Chiu, N. Hori, and L.W. Weiss, FACSM.

Abstract
PURPOSE: To determine the effects of astaxanthin anti-oxidant supplementation as a counter-measure for delayed onset muscular soreness (DOMS) in currently trained individuals, nine weight trained males (X+SE: age=25.1+1.6 yrs., hgt=1.79+0.02 m, wgt=86.8+4.4 kg) participated in this study. METHODS: All subjects provided muscle biopsy samples from the vastus lateralis m. prior to inducing DOMS in the knee extensor mm. (10 sets x 7-10 reps, 85% eccentric 1 RM). The subjects ingested either 4 mg.d-1 of astaxanthin (Suppl; n=4) or a placebo (Con; n=5) for a 3 week loading phase prior to the DOMS-inducing protocol, and during a 12 d recovery phase. Perceptions of DOMS at 48 hrs post-eccentric exercise were quantified by muscle soreness ratings (0-10 Likert scale). Muscle fiber characteristics were determined via mATPase histochemistry and digital imaging to determine % cross-sectional areas of the major fiber types (I, IIA, IIAB/B). Due to small numbers of IIB fibers in some subjects, IIAB hybrid fibers were included in this fiber type population. Simple regression was used to determine relationships between fiber characteristics and perceptions of soreness. RESULTS: No differences in perceptions of soreness between the Suppl or Con groups were observed ($p>0.05$), with all subjects exhibiting a mean score of >5. Percent fiber type areas were similar ($p>0.05$) for both groups (type I, Suppl=47.6+8.9%, Con=41.3+2.7%; type IIA, Suppl=44.3+5.6%, Con=53.0+2.8%; type IIAB/B, Suppl=8.2+3.6%, Con=5.7+1.6%). However, 48 hrs after the DOMS-inducing session, perceptions of soreness for the Suppl group were positively related to % area type I ($r=0.90$), and negatively related to % area types IIA ($r=-0.80$) and IIAB/B ($r=-0.99$). A distinctly different correlational pattern was observed for the Con group (% type I area, $r=-0.58$; % type IIA area, $r=0.32$; % type IIAB/B area, $r=0.40$). CONCLUSIONS: Collectively, these preliminary data suggest that astaxanthin supplementation may preferentially attenuate perceptions of DOMS in weight trained men with a high % area for fiber types IIA & AB/B.

Hiro to Kyuyo no Kagaku VOL.18;NO.1;PAGE.35-46(2003)

Effects of Astaxanthin on Recovery from Whole Fatigue with Three Stepwise Exercises

NAGATA AKIRA; TAJIMA TAEKO; HAMAMATSU HOZUMI

This study was designed to evaluate the effects of astaxanthin (A) ingestion upon recovery from whole fatigue, that were generated by progressive loads of three stepwise exercise-30%HRmax, 50%HRmax, and 70%HRmax. Nineteen healthy volunteers were randomized into two groups: Group A (10 subjects) received oral astaxanthin capsule (5mg) daily for two weeks, while Group C (9 subjects) ingested oral placebo (C) capsule (5mg) with the double blind method. After a month from this ingestion, another capsules were taken again with cross-over system for the same subjects respectively. Comparative detections were practiced to estimate with effectiveness of A ingestion upon changing ratios between two groups. Significant difference between A and C groups were obtained to inhibit the increase of respiratory-circulatory function from expired gases analysis. Additionally sympathetic nervous activities (LF/HF ratio) during exercise and parasympathetic nervous activities (HF/TF 100) during recovery were observed to significant increase. Otherwise, blood serum concentration of LDL cholesterols showed significant decrease, while concentration of creatine phosphokinase had increased to higher level than that of C ingestion, significantly. Then, findings of the present study indicated that with astaxanthin ingestion for human, respiratory-circulation ability and activities of sympathetic nervous system were augmented to make efficient metabolism during exercise load. Those anti-fatigue and anti-oxidative function might be promoted for human to make recovery ability from the whole fatigue generated by exercise stress.

Japanese Journal of Physical Fitness and Sports Medicine. Vol. 54, No. 6, pg 466. December 2005.

Effect of Astaxanthin on Muscular Atrophy

Tateo Sugiura, Yoshiharu Iida, Hisashi Naito, Daijiro Ohmori, Katsumasa Goto, Toshitada Yoshioka

Objective: Patients wearing casts or other devices that hinder mobility are reported to have muscular atrophy. It is commonly thought that the cause is from reactive oxygen species (ROS). The use of Vitamin E, along with other antioxidants, prevents ROS from causing muscular atrophy that arises from lack of movement; however there has been conflicting reports on its effectiveness, varying from some claiming that it works and others that it does not.

Results and Analysis: Groups that were administered Ax had significantly less muscle atrophy than those in the Control group ($p<0.05$). The level of Cu/Zn-SOD expressed was higher in the rats with casts than those without casts in the control group; however, in the Ax group, the level expressed was insignificantly different from those with casts and those without. In addition, the level expressed in the control group with casts was significantly higher than the Ax group with casts on. The level of calpain and ubiquitin expressed was higher in the control group with casts than those in the Ax group with casts, but the difference was insignificant. Also, significantly less (of calpain and ubiquitin) was expressed in the Ax 0.2% with casts compared to the control group with casts. The same pattern was seen with Capthesin L expression.
Presently, it is reported that muscular atrophy in patients who are immobile due to casts was caused by oxidative stress. The increase in oxidative stress accelerates the reaction of lipoperoxide, which causes distress in the cell membrane and sarcoendoplaxmic reticulum, leading to an increase in Ca2+ in the cytoplasm and concurrently causing a decrease in its discharge. An increase in Ca2+ concentration activates calpain along with cathepsin. In addition, the presence of lipoperoxide causes disruption in the cell membrane of the mitrocondria, causing iron ions and ROS to leak in the cytoplasm, which leads to ubiquitination (of proteins.) Ax is the same as beta-carotene in that they are both carotenoids. They both prevent lipoperoxides from disturbing the cell membrane in many biological organisms, but Ax is more active than other antioxidants. Based on this information, we believe Ax intake prevents muscular atrophy by protecting membranes; preventing oxidative stress which results in atrophy; preventing the facilitation protease and ubiquitination. The effects due to the quantity of Ax uptake were not clear in this study.

Applications for Athletes: Muscular Atrophy

Long term dietary antioxidant intakes attenuate sarcopenia

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Japanese Journal of Physical Fitness and Sports Medicine. 2008, 57:541-52

Oxidative stress is thought to be one of significant contributing factors to age-related sarccpenia. We tested the hypothesis that the long term dietary antioxidant (astaxanthin intakes attenuate sarcopenie. Wistar strain male rats, aged 45 weeks old, were given either control (Cont) or astaxanthin feed (0.004%, Ax) for 1 year. 'The soleus muscle weights and muscle weigh-to-body weight ratios in Ax group were significantly heavier than in Cont group, but tibialis anterior muscle mass remained similar between the two dietary groups. The level of ubiquitinated proteins was significantly lower in soleus muscles of Ax group, but not in tibialis anterior muscles when compared with Cont group. Tibialis anterior levels of cathepsin Land caepase-S were tended to be lower in Ax group than in Cont group, especially significant differences observed in cathepsin L, whereas no differences between Cont and Ax were observed in soleus tbcae levels. There woro no effects of Ax supplementation on calpaia 1 and 2, UBC3B, CulZn SOD and nitrotyrosine levels in both soleus and tibialis anterior muscles. OUT data suggest that the long term dietary astaxanthin intakes attenuate the age related muscle atrophy, due in part, to reductions in oxidative stress and ubiquitination of myofibrillar protein in slow soleus muscles, but not in fast tibialis anterior muscles.

Carotenoid Science, Vol.13, 2008 ISSN 1880-5671

Dietary Supplementation with Astaxanthin-Rich Algal Meal Improves Strength Endurance – A Double Blind Placebo Controlled Study on Male Students

Curt L. Malmsten and Åke Lignell

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.

Title;Effects of Astaxanthin Supplementation on Exercise-Induced Fatigue in Mice

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Figure&Table&Reference;FIG.6, REF.22

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Language;English

Abstract;The present study was designed to determine the effect of astaxanthin on endurance capacity in male mice aged 4 weeks. Mice were given orally either vehicle or astaxanthin (1.2, 6, or 30 mg/kg body weight) by stomach intubation for 5 weeks. The astaxanthin group showed a significant increase in swimming time to exhaustion as compared to the control group. Blood lactate concentration in the astaxanthin groups was significantly lower than in the control group. In the control group, plasma non-esterfied fatty acid (NEFA) and plasma glucose were decreased by swimming exercise, but in the astaxanthin group, NEFA and plasma glucose were significantly higher than in the control group. Astaxanthin treatment also significantly decreased fat accumulation. These results suggest that improvement in swimming endurance by the administration of astaxanthin is caused by an increase in utilization of fatty acids as an energy source.

Effects of Astaxanthin Ingestion on Exercise-Induced Physiological Changes

Authors: Taeko Tajima, Akira Nagata. **Health and Behavior Sciences.,3(1):5-10(2004).**

Abstract

The purpose of this study was to evaluate the effects of astaxantin (ACT) ingestion on exercise-induced physiological functions. In this experiment we planned to investigate the autonomic nervous system (ANS) and the respiratory metabolism during different exercise intensities in subjects taking astaxantin and those taking placebo. The design of this experiment was a double-blind crossover study.

Eighteen male volunteers (35.8 $\pm$ 4.51 years of age) took ACT or placebo (CON) capsule daily for two weeks. Exercise stress tests were done before and after the ingestion period. The exercise load was in the form of running exercise on a treadmill at intensities of 30%, 50% and 70% of maximum heart rate (HRmax). Heart rate variability (HRV), expired gases analysis and blood biochemical parameters were measured. Sympathetic nervous activity (SNA) and parasympathetic nervous activity (PNA) were estimated from the pattern of power density in three frequency ranges on the power spectrum.

During the exercise at an intensity of 70% HRmax, CV_{RR} and HF/TF increased significantly ($p<0.05$) after ACT ingestion. Additionally, V_E decreased significantly ($p<0.05$) during exercise at 70% HRmax after ACT ingestion. These data indicated that after ACT ingestion, SNA was decreased and PNA was enhanced during exercises at 70% HRmax. Furthermore LDL cholesterol decreased markedly after exercise ($p<0.05$) and respiratory quotient decreased during exercise. These results suggest that ACT may contribute to enhancement of lipid metabolism. Decrease of respiratory parameters may indicate augmentation of the efficacy of exercise in energy metabolism.

Applications for Athletes: Energy Metabolism

Additional Areas of Research

J. Nat. Prod. **2006,** *69,* 443-449

Astaxanthin, a Carotenoid with Potential in Human Health and Nutrition

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Astaxanthin (1), a red-orange carotenoid pigment, is a powerful biological antioxidant that occurs naturally in a wide variety of living organisms. The potent antioxidant property of 1 has been implicated in its various biological activities demonstrated in both experimental animals and clinical studies. Compound 1 has considerable potential and promising applications in human health and nutrition. In this review, the recent scientific literature (from 2002 to 2005) is covered on the most significant activities of 1, including its antioxidative and anti-inflammatory properties, its effects on cancer, diabetes, the immune system, and ocular health, and other related aspects. We also discuss the green microalga Haematococcus pluVialis, the richest source of natural 1, and its utilization in the promotion of human health, including the antihypertensive and neuroprotective potentials of 1, emphasizing our experimental data on the effects of dietary astaxanthin on blood pressure, stroke, and vascular dementia in animal models, is described.

Recenti Prog Med. 2010 Apr;101(4):145-56.

[Omega-3 fatty acids and astaxanthin in health and disease. Recent knowledges]

[Article in Italian]

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Erratum in:

- Recenti Prog Med. 2010 May;101(5):180.

Abstract

At present, medicine is aimed to the treatment of lesions. Instead, it would be right to develop the maintenance of normal health. A number of authorities have recently recommended increases in intake of omega-3 fatty acids and astaxanthin for the health of general population. Omega-3 are necessary to provide the optimal function of cellular membrane in health and in disease states. It is well known how at least two servings of fish a week, or dietary supplementation of fatty acids omega-3, should be taken to obtain the health benefits of this essential nutrient. Astaxanthin is a powerful biological antioxidant. This property has been implicated in its various biological activities demonstrated in both experimental animals and clinical studies. For the recent evidence of the contemporary presence of omega-3 and astaxanthin in oil of Wild Pacific Salmon Sockeye, a review has been effected for the evaluation of a possible role of such association for the health promotion.

PMID: 20540399 [PubMed - indexed for MEDLINE]

Critical Reviews in Food Science and Nutrition, 46:185–196 (2006) ISSN: 1040-8398

Astaxanthin: A Review of its Chemistry and Applications

HIGUERA-CIAPARA, L. FE´ LIX-VALENZUELA, and F. M. GOYCOOLEA

Astaxanthin is a carotenoid widely used in salmonid and crustacean aquaculture to provide the pink color characteristic of that species. This application has been well documented for over two decades and is currently the major market driver for the pigment. Additionally, astaxanthin also plays a key role as an intermediary in reproductive processes. Synthetic astaxanthin dominates the world market but recent interest in natural sources of the pigment has increased substantially. Common sources of natural astaxanthin are the green algae Haematococcus pluvialis, the red yeast, Phaffia rhodozyma, as well as crustacean byproducts. Astaxanthin possesses an unusual antioxidant activity which has caused a surge in the nutraceutical market for the encapsulated product. Also, health benefits such as cardiovascular disease prevention, immune system boosting, bioactivity against Helycobacter pylori, and cataract prevention, have been associated with astaxanthin consumption. Research on the health benefits of astaxanthin is very recent and has mostly been performed in vitro or at the pre-clinical level with humans. This paper reviews the current available evidence regarding astaxanthin chemistry and its potential beneficial effects in humans.

Additional Areas of Research: General Health

Trends Biotechnol. 2003 May;21(5):210-6.

Haematococcus astaxanthin: applications for human health and nutrition

Martin Guerin, Mark E, Huntley and Miguel Olaizola

The carotenoid pigment astaxanthin has important applications in the nutraceutical, cosmetics, food and feed industries. Haematococcus pluvialis is the richest source of natural astaxanthin and is now cultivated at industrial scale. Astaxanthin is a strong coloring agent and a potent antioxidant - its strong antioxidant activity points to its potential to target several health conditions. This article covers the antioxidant, UV-light protection, anti-inflammatory and other properties of astaxanthin and its possible role in many human health problems. The research reviewed supports the assumption that protecting body tissues from oxidative damage with daily ingestion of natural astaxanthin might be a practical and beneficial strategy in health management.

Additional Areas of Research: General Health

ASTAXANTHIN
Continuing Education Module

by Timothy J. Maher, Ph.D.

Goal:
The goal of this module is to introduce the reader to the carotenoid astaxanthin and examine its antioxidant actions especially as it relates to potential therapeutic approaches in addressing cardiovascular disease, neurodegenerative disease, cancer, immune function status and visual health.

Objectives:
Following successful completion of this module, the participant will be able to:
• describe the unique antioxidant features of the carotenoid astaxanthin;
• list the sources in nature and the functions of astaxanthin in animals that produce and consume astaxanthin;
• explain findings of recent research that describe the effects of astaxanthin in cardiovascular disease, neurodegenerative
disease, visual health, cancer and immune system function;
• describe the pharmacokinetics of astaxanthin and list its potential side effects.

Haematococcus astaxanthin: health and nutritional applications

Martin Guerin, Mark E. Huntley, Miguel Olaizola
Mera Pharmaceuticals, Inc.

This review was presented at the 1st Congress of the International Society for Applied Phycology/9th International Conference on Applied Phycology May 26-30, 2002, Almeria, Spain

Abstract

Astaxanthin, a carotenoid pigment, has important applications in the nutraceutical, cosmetics, food and feed industries. Haematococcus pluvialis is the richest source of natural astaxanthin and is now cultivated at industrial scale. Astaxanthin is a strong coloring agent and a potent antioxidant. Astaxanthin.s strong antioxidant activity points to its potential to target a number of health conditions. Here we review the scientific literature on antioxidant, UV-light protection, and anti-inflammatory properties of astaxanthin, and its possible role in cellular health, cancer, immunology, liver function, heart health, eye health, central nervous system health, and other human health concerns. We also report results of a survey among users of a commercially available astaxanthin product (AstaFactor□). A detailed health questionnaire was mailed to 758 users of AstaFactor□ of which 247 responses were returned. The respondents. age ranged from 20 to 87 years old. The reported effects of AstaFactor□ supplementation conform to expectations of astaxanthin activity in chemical and animal models. Eighty eight percent of respondents reporting that they suffer from sore muscles or joints, observed a reduction in soreness or pain. Similarly, over 80% of those reporting back pain and symptoms from osteoarthritis or rheumatoid arthritis reported an improvement from
astaxanthin supplementation. Astaxanthin supplementation was also reported to improve symptoms of asthma and enlarged prostate. All of these conditions have an inflammation component which is closely tied to oxidative damage. These results support the assumption that protecting body tissues from oxidative damage with daily ingestion of natural astaxanthin may be a practical and beneficial strategy in health management.

Additional Areas of Research: General Health

Biosci Biotechnol Biochem. 2007 Apr;71(4):893-9. Epub 2007 Apr 7.

Effects of astaxanthin in obese mice fed a high-fat diet.

Ikeuchi M, **Koyama T**, **Takahashi J**, **Yazawa K**.

Laboratory of Nertraceuticals and Functional Foods Science, Graduate School of Marine Science and Technology, Tokyo University of Marine Science and Technology, Tokyo, Japan.

Astaxanthin is a natural antioxidant carotenoid that occurs in a wide variety of living organisms. We investigated the effects of astaxanthin supplementation in obese mice fed a high-fat diet. Astaxanthin inhibited the increases in body weight and weight of adipose tissue that result from feeding a high-fat diet. In addition, astaxanthin reduced liver weight, liver triglyceride, plasma triglyceride, and total cholesterol. These results suggest that astaxanthin might be of value in reducing the likelihood of obesity and metabolic syndrome in affluent societies.

PMID: 17420580 [PubMed - indexed for MEDLINE]

Methods Find Exp Clin Pharmacol. 2001 Mar;23(2):79-84.

Effect of astaxanthin on the hepatotoxicity, lipid peroxidation and antioxidative enzymes in the liver of CCl4-treated rats.

Kang JO, **Kim SJ**, **Kim H**.

Department of Food and Nutrition, College of Human Ecology, Seoul National University, Korea.

Astaxanthin is one of many carotenoids present in marine animals, vegetables and fruits. Since carotenoids are known to have antioxidant properties, we tested to determine if astaxanthin could have protective effects in the CCl4-treated rat liver by activating the antioxidant system. Astaxanthin blocked the increase of glutamate-oxalacetate transaminase (GOT) and glutamate-pyruvate transaminase (GTP) activity and thiobarbituric acid reactive substances (TBARS) in response to carbon tetrachloride (CCl4), while causing an increase in glutathione (GSH) levels and superoxide dismutase (SOD) activities in the CCl4-treated rat liver. These results suggest that astaxanthin protects liver damage induced by CCl4 by inhibiting lipid peroxidation and stimulating the cellular antioxidant system.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 11484414 [PubMed - indexed for MEDLINE]

Additional Areas of Research: Hepatoprotective (Liver)

Xenobiotica. 1996 Sep;26(9):909-19.

beta-Apo-8'-carotenal, but not beta-carotene, is a strong inducer of liver cytochromes P4501A1 and 1A2 in rat.

Gradelet S, **Leclerc J**, **Siess MH**, **Astorg PO**.

Unité de Toxicologie Nutritionnelle, Institut National de la Recherche Agronomique, Dijon, France.

1. The catalytic activities of several phase I and II xenobiotic-metabolizing enzymes and their immunochemical detection have been investigated in liver microsomes and cytosol of the male rat, which had been fed for 15 days with diets containing 300 mg/kg beta-carotene isomers (all-trans beta-carotene or beta-carotene from Dunaliella salina rich in 9-cis isomer or isomerized beta-carotene), or apocarotenoids as beta-apo-8'-carotenal, ethyl beta-apo-8'-carotenoate and citranaxanthin. 2. Beta-carotene, either all-trans or containing cis isomers, did not induce any significant change in the measured activities. By contrast, beta-apo-8'-carotenal increased the liver content of cytochrome P450, the activity of NADH- and NADPH-cytochrome c reductase, and strongly increased some cytochrome P450-dependent activities, particularly ethoxyresorufin O-deethylase (x158), methoxyresorufin O-demethylase (x22), pentoxy- and benzoxyresorufin O-dealkylases, but did not affect erythromycin N-demethylase nor nitrosodimethylamine N-demethylase activities. Phase II p-nitrophenol- and 4-hydroxy- biphenyl-uridine diphosphoglucuronosyl transferase activities were also increased by beta-apo-8'carotenal. Western blots of microsomal proteins clearly showed the induction of CYP1A1 and 1A2 by beta-apo-8'-carotenal. This induction profile resembles that produced by two other carotenoids: canthaxanthin and astaxanthin. Ethyl beta-apo-8'-carotenoate and citranaxanthin showed similar effects to beta-apo-8'-carotenal but of less intensity. 3. Three carotenoids: beta-apo-8'-carotenal, canthaxanthin and astaxanthin, are inducers of CYP1A1 and 1A2 in the rat. These carotenoids form a new class of inducers of CYP1A, structurally very different from the classical inducers as 3-methylcholanthrene, beta-naphtoflavone or dioxin.

Publication Types:

- Research Support, Non-U.S. Gov't

PMID: 8893038 [PubMed - indexed for MEDLINE]

Additional Areas of Research: Hepatoprotective (Liver)

Toxicology. 2010 Jan 12;267(1-3):147-53. Epub 2009 Nov 10.

Effect of astaxanthin on hepatocellular injury following ischemia/reperfusion.

Curek GD, Cort A, Yucel G, Demir N, Ozturk S, Elpek GO, Savas B, Aslan M.

Department of Biochemistry, Akdeniz University Medical School, Antalya 07070, Turkey.

Abstract

This study investigated the effect of astaxanthin (ASX; 3,3-dihydroxybeta, beta-carotene-4,4-dione), a water-dispersible synthetic carotenoid, on liver ischemia-reperfusion (IR) injury. Astaxanthin (5 mg/kg/day) or olive oil was administered to rats via intragastric intubation for 14 consecutive days before the induction of hepatic IR. On the 15th day, blood vessels supplying the median and left lateral hepatic lobes were occluded with an arterial clamp for 60 min, followed by 60 min reperfusion. At the end of the experimental period, blood samples were obtained from the right ventricule to determine plasma alanine aminotransferase (ALT) and xanthine oxidase (XO) activities and animals were sacrificed to obtain samples of nonischemic and postischemic liver tissue. The effects of ASX on IR injury were evaluated by assessing hepatic ultrastructure via transmission electron microscopy and by histopathological scoring. Hepatic conversion of xanthine dehygrogenase (XDH) to XO, total GSH and protein carbonyl levels were also measured as markers of oxidative stress. Expression of NOS2 was determined by immunohistochemistry and Western blot analysis while nitrate/nitrite levels were measured via spectral analysis. Total histopathological scoring of cellular damage was significantly decreased in hepatic IR injury following ASX treatment. Electron microscopy of postischemic tissue demonstrated parenchymal cell damage, swelling of mitochondria, disarrangement of rough endoplasmatic reticulum which was also partially reduced by ASX treatment. Astaxanthine treatment significantly decreased hepatic conversion of XDH to XO and tissue protein carbonyl levels following IR injury. The current results suggest that the mechanisms of action by which ASX reduces IR damage may include antioxidant protection against oxidative injury.

PMID: 19900500 [PubMed - indexed for MEDLINE

Additional Areas of Research: Hepatoprotective (Liver)

Xenobiotica. 1996 Jan;26(1):49-63.

Effects of canthaxanthin, astaxanthin, lycopene and lutein on liver xenobiotic-metabolizing enzymes in the rat.

Gradelet S, **Astorg P**, **Leclerc J**, **Chevalier J**, **Vernevaut MF**, **Siess MH**.

Unité de Toxicologie Nutritionnelle, Institut National de la Recherche Agronomique, DIJON, France.

1. The catalytic activities of several phase I and II xenobiotic-metabolizing enzymes and the immunochemical detection of P4501A and 2B have been investigated in liver microsomes and cytosol of male rats fed for 15 days with diets containing canthaxanthin, astaxanthin, lycopene or lutein (as lutein esters) (300 mg/kg diet) and in rats fed increasing levels (10, 30, 100 and 300 ppm) of canthaxanthin or astaxanthin in the diet. 2. Canthaxanthin increased the liver content of P450, the activities of NADH- and NADPH-cytochrome c reductase, and produced a substantial increase of some P450-dependent activities, especially ethoxyresorufin O-deethylase (EROD) (x 139) and methoxyresorufin O-demethylase (MROD) (x 26). Canthaxanthin also increased pentoxy-(PROD) and benzoxyresorufin O-dealkylases (BROD), but did not affect. NADPH-cytochrome c reductase and erythromycin N-demethylase (ERDM) activities and decreased nitrosodimethylamine N-demethylase (NDMAD) activity. Phase II p-nitrophenol UDP-glucuronosyl transferase (4NP-UGT) and quinone reductase (QR) activities were also increased by canthaxanthin treatment. These enhancing effects on EROD, MROD and 4NP-UGT were clearly detectable at a dose as low as 10 ppm of canthaxanthin in the diet; the induction of QR was only observed in rats fed > or = 100 ppm. Astaxanthin induced the same pattern of enzymes activities as canthaxanthin, but to a lesser extent: its effects on phase I enzymes and 4NP-UGT were observed in rats fed > or = 100 ppm, and QR was not increased. Western blots of microsomal proteins clearly showed the induction of P4501A1 and 1A2 by canthaxanthin and astaxanthin. By contrast, lutein had no effect on the phase I and II xenobiotic-metabolizing enzymes activities measured. Lycopene only decreased NDMAD activity. 3. The two 4-oxocarotenoids canthaxanthin and astaxanthin are substantial inducers of liver P4501A1 and 1A2 in the rat, and coinduce 4NP-UGT and QR, just like polycyclic aromatic hydrocarbon, beta-naphtoflavone or dioxin (TCDD). However, these latter classical P4501A inducers also induce aldehyde dehydrogenase class 3 (ALDH3); this enzyme is not increased, or only marginally, by canthaxanthin and astaxanthin. These two oxocarotenoids form a new class of inducers of P4501A, are structurally very different from the classical inducers quoted above, which are ligands of the AH receptor.

Publication Types:

- In Vitro
- Research Support, Non-U.S. Gov't

PMID: 8851821 [PubMed - indexed for MEDLINE]

Additional Areas of Research: Hepatoprotective (Liver)

Food Chem Toxicol. 2008 Jan;46(1):212-9. Epub 2007 Aug 14.

Effect of astaxanthin on kidney function impairment and oxidative stress induced by mercuric chloride in rats.

Augusti PR, **Conterato GM**, **Somacal S**, **Sobieski R**, **Spohr PR**, **Torres JV**, **Charão MF**, **Moro AM**, **Rocha MP**, **Garcia SC**, **Emanuelli T**.

Post-graduate Program on Toxicological Biochemistry, Center of Natural and Exact Sciences, Federal University of Santa Maria, 97105-900 Santa Maria, RS, Brazil.

Reactive oxygen species are implicated as mediators of tissue damage in the acute renal failure induced by inorganic mercury. Astaxanthin (ASX), a carotenoid with potent antioxidant properties, exists naturally in various plants, algae, and seafoods. This paper evaluated the ability of ASX to prevent HgCl(2) nephrotoxicity. Rats were injected with HgCl(2) (0 or 5 mg/kg b.w., sc) 6h after ASX had been administered (0, 10, 25, or 50mg/kg, by gavage) and were killed 12h after HgCl(2) exposure. Although ASX prevented the increase of lipid and protein oxidation and attenuated histopathological changes caused by HgCl(2) in kidney, it did not prevent creatinine increase in plasma and delta-aminolevulinic acid dehydratase inhibition induced by HgCl(2). Glutathione peroxidase and catalase activities were enhanced, while superoxide dismutase activity was depressed in HgCl(2)-treated rats when compared to control and these effects were prevented by ASX. Our results indicate that ASX could have a beneficial role against HgCl(2) toxicity by preventing lipid and protein oxidation, changes in the activity of antioxidant enzymes and histopathological changes.

Publication Types:

PMID: 17881112 [PubMed - indexed for MEDLINE]

Additional Areas of Research: Renal Protective (Kidney)

J Herb Pharmacother. 2005;5(1):17-26.

A preliminary investigation of the enzymatic inhibition of 5alpha-reduction and growth of prostatic carcinoma cell line LNCap-FGC by natural astaxanthin and Saw Palmetto lipid extract in vitro.

Anderson ML.

Research and Development, Triarco Industries, Wayne, NJ 07470, USA. mark.anderson@triarco.com

Inhibition of 5alpha-reductase has been reported to decrease the symptoms of benign prostate hyperplasia (BPH) and possibly inhibit or help treat prostate cancer. Saw Palmetto berry lipid extract (SPLE) is reported to inhibit 5alpha-reductase and decrease the clinical symptoms of BPH. Epidemiologic studies report that carotenoids such as lycopene may inhibit prostate cancer. In this investigation the effect of the carotenoid astaxanthin, and SPLE were examined for their effect on 5alpha-reductase inhibition as well as the growth of prostatic carcinoma cells in vitro. These studies support patent #6,277,417 B1. The results show astaxanthin demonstrated 98% inhibition of 5alpha-reductase at 300 microg/mL in vitro. Alphastat, the combination of astaxanthin and SPLE, showed a 20% greater inhibition of 5alpha-reductase than SPLE alone n vitro. A nine day treatment of prostatic carcinoma cells with astaxanthin in vitro produced a 24% decrease in growth at 0.1 mcg/mL and a 38% decrease at 0.01 mcg/mL. SPLE showed a 34% decrease at 0.1 mcg/mL. CONCLUSIONS: Low levels of carotenoid astaxanthin inhibit 5alpha-reductase and decrease the growth of human prostatic cancer cells in vitro. Astaxanthin added to SPLE shows greater inhibition of 5alpha-reductase than SPLE alone in vitro.

Publication Types:

- In Vitro

PMID: 16093232 [PubMed - indexed for MEDLINE]

Additional Areas of Research: Prostate Health

Reprod Biomed Online. 2003 Oct-Nov;7(4):385-91.

The role of food supplements in the treatment of the infertile man.

Comhaire FH, **Mahmoud A**.

Centre for Medical and Urological Andrology, Ghent University Hospital, De Pintelaan, 185, B 9000 Gent, Belgium. frank.comhaire@rug.ac.be

Recently, concerns have been raised about the presumptive increased risk of serious undesirable side effects in children born after IVF and intracytoplasmic sperm injection (ICSI). These treatments must, therefore, be reserved as the ultimate option after evidence-based and cause-directed treatment of the male patient with deficient semen has been exhausted. The present authors found that sperm quality and function improved with the intake of complementary food supplementation using a combination of zinc and folic acid, or the antioxidant astaxanthin (Astacarox), or an energy-providing combination containing (actyl)-carnitine (Proxeed). Also, double blind trials showed that the latter two substances increase spontaneous or intrauterine insemination- (IUI-) assisted conception rates. Extracts of Pinus maritima bark (Pycnogenol), which inhibits the cyclo-oxygenase enzyme, reducing prostaglandin production and inflammatory reaction, and extracts of the Peruvian plant Lepidium meyenii were shown to improve sperm morphology and concentration, respectively, in uncontrolled trials. Linseed (flaxseed) oil contains alfa-linolenic acid and lignans. The former corrects the deficient intake of omega-3 essential fatty acids, which is correlated with impaired sperm motility among subfertile men. Lignans are precursors of enterolacton, which inhibits aromatase and reduces the ratio of 16-OH over 2-OH oestrogen metabolites. The resulting reduction in oestrogen load may favourably influence Sertoli cell function.

PMID: 14656398 [PubMed - indexed for MEDLINE]

Additional Areas of Research: Male Fertility

Asian J Androl. 2005 Sep;7(3):257-62.

Combined conventional/antioxidant "Astaxanthin" treatment for male infertility: a double blind, randomized trial.

Comhaire FH, **El Garem Y**, **Mahmoud A**, **Eertmans F**, **Schoonjans F**.

Ghent University Hospital, Department of Medical and Urological Andrology, 9k12 IE, De Pintelaan, 185, B 9000, Gent, Belgium. frank.comhaire@ugent.be

AIM: To evaluate the treatment of male infertility with a strong natural antioxidant, in addition to conventional treatment. METHODS: Using a double blind, randomized trial design, 30 men with infertility of > or =2 months and female partners with no demonstrable cause of infertility received conventional treatment according to the guidelines of the World Health Organization (WHO), and either a strong antioxidant Astaxanthin 16 mg/day (AstaCarox, AstaReal AB, Gustavsberg, Sweden) or placebo for 3 months. The effects of treatment on semen parameters, reactive oxygen species (ROS), zona-free hamster oocyte test, serum hormones including testosterone, luteinizing hormone (LH), follicle stimulating hormone (FSH) and Inhibin B, and spontaneous or intrauterine insemination (IUI)-induced pregnancies were evaluated. RESULTS: ROS and Inhibin B decreased significantly and sperm linear velocity increased in the Astaxanthin group (n = 11), but not in the placebo group (n = 19). The results of the zona-free hamster oocyte test tended to improve in the Astaxanthin group in contrast with the placebo group, though not reaching statistical significance. The total and per cycle pregnancy rates among the placebo cases (10.5 % and 3.6 %) were lower compared with 54.5 % and 23.1 % respectively in the Astaxanthin group (P = 0.028; P = 0.036). CONCLUSION: 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.

Publication Types:

- Clinical Trial
- Randomized Controlled Trial
- Research Support, Non-U.S. Gov't

PMID: 16110353 [PubMed - indexed for MEDLINE]

Additional Areas of Research: Male Fertility

Asian J Androl. 2005 Sep;7(3):257-62

Semen and Fertility Abstracts for Astaxathin

Comhaire FH, El Garem Y, Mahmoud A, Eertmans F, Schoonjans F.

To evaluate the treatment of male infertility with a strong natural antioxidant, in addition to conventional treatment. METHODS: Using a double blind, randomized trial design, 30 men with infertility of > or =2 months and female partners with no demonstrable cause of infertility received conventional treatment according to the guidelines of the World Health Organization (WHO), and either a strong antioxidant Astaxanthin 16 mg/day (AstaCarox, AstaReal AB, Gustavsberg, Sweden) or placebo for 3 months. The effects of treatment on semen parameters, reactive oxygen species (ROS), zona-free hamster oocyte test, serum hormones including testosterone, luteinizing hormone (LH), follicle stimulating hormone (FSH) and Inhibin B, and spontaneous or intrauterine insemination (IUI)-induced pregnancies were evaluated. RESULTS: ROS and Inhibin B decreased significantly and sperm linear velocity increased in the Astaxanthin group (n = 11), but not in the placebo group (n = 19). The results of the zona-free hamster oocyte test tended to improve in the Astaxanthin group in contrast with the placebo group, though not reaching statistical significance. The total and per cycle pregnancy rates among the placebo cases (10.5 % and 3.6 %) were lower compared with 54.5 % and 23.1 % respectively in the Astaxanthin group (P = 0.028; P = 0.036). CONCLUSION: 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

XIII International Carotenoid Symposiumm Hawaii January **2002**. Patent Cooperation Treaty Application WO99 / 29313. AstaCarotene AB, Sweden.

Natural Astaxanthin Improves Semen Quality in Infertile Men

GAREM, Y.E., A. LIGNELL u. F. COMHAIRE

Natural Astaxanthin from Haematococcus Algae has been shown in a double blind, placebo controlled clinical to improve fertility in infertile men. Natural Astaxanthin had previously been shown to improve fertility in male animals such as boars and stallions. This study was conducted on men who were diagnosed as infertile due to abnormal sperm quality. The experimental group received 16 mg of Natural Astaxanthin per day for three months. The results were an improvement in conception rate in the experimental group by 478% over the placebo group. The scientist concluded that supplementation with Natural Astaxanthin improved the quality of the spermatozoa, which is suggested to be the plausible explanation for the increased frequency of conception.*

Additional Areas of Research: Male Fertility

Phytother Res. 2010 Jul 14. [Epub ahead of print]

Summative interaction between astaxanthin, Ginkgo biloba extract (EGb761) and vitamin C in Suppression of respiratory inflammation: a comparison with ibuprofen.

Haines DD, Varga B, Bak I, Juhasz B, Mahmoud FF, Kalantari H, Gesztelyi R, Lekli I, Czompa A, Tosaki A.

Department of Pharmacology, Faculty of Pharmacy, University of Debrecen, Debrecen, Hungary.

Abstract

In this study, combinations of Ginkgo biloba leaf extract (EGb761) plus the carotenoid antioxidant astaxanthin (ASX) and vitamin C were evaluated for a summative dose effect in the inhibition of asthma-associated inflammation in asthmatic guinea-pigs. Ovalbumin-sensitized Hartley guinea-pigs challenged with ovalbumin aerosol to induce asthma, were administered EGb761, ASX, vitamin C or ibuprofen. Following killing, bronchoalveolar lavage (BAL) fluid was evaluated for inflammatory cell infiltrates and lung tissue cyclic nucleotide content. Each parameter measured was significantly altered to a greater degree by drug combinations, than by each component acting independently. An optimal combination was identified that included astaxanthin (10 mg/kg), vitamin C (200 mg/kg) and EGb761 (10 mg/kg), resulting in counts of eosinophils and neutrophils each 1.6-fold lower; macrophages 1.8-fold lower, cAMP 1.4-fold higher; and cGMP 2.04-fold higher than levels in untreated, asthmatic animals ($p < 0.05$). In conclusion, EGb761, ASX and vitamin C are shown here to interact summatively to suppress inflammation with efficacy equal to or better than ibuprofen, a widely used non-steroidal antiinflammatory drug (NSAID). Such combinations of non-toxic phytochemicals constitute powerful tools for the prevention of onset of acute and chronic inflammatory disease if consumed regularly by healthy individuals; and may also augment the effectiveness of therapy for those with established illness.

PMID: 20632299 [PubMed - as supplied by publisher]

Additional Areas of Research: Asthma

J Pharmacol Sci. 2004 Feb;94(2):129-36.

In vitro effects of astaxanthin combined with ginkgolide B on T lymphocyte activation in peripheral blood mononuclear cells from asthmatic subjects.

Mahmoud FF, **Haines DD**, **Abul HT**, **Abal AT**, **Onadeko BO**, **Wise JA**.

Department of Medical Laboratory Sciences, Faculty of Allied Health Sciences, Kuwait University, Sulaibikhat. fadia@hsc.kuniv.edu.kw

This study was undertaken to identify novel approaches to pharmacological treatment of asthma. Here we hypothesize that the platelet-activating factor receptor antagonist ginkgolide B (GB) in combination with the antioxidant carotenoid astaxanthin (ASX) suppresses T cell activation comparably to two commonly-used antihistamines: cetirizine dihydrochloride (CTZ) and azelastine (AZE). Peripheral blood mononuclear cells from asthmatics, cultured 24 h with either 50 microg/ml phytohemaglutinin (PHA) or PHA plus selected dosages of each drug are analyzed by flow cytometry for CD25+ or HLA-DR+ on CD3+ (T cells). Results are reported as stimulation indices (SI) of %CD3+CD25+ cells or %CD3+HLA-DR+ cells in cultures treated with PHA alone versus these subpopulations in cultures treated with both PHA and drugs. Combinations of ASX and GB exhibited optimal suppression at 10(-7) M GB + 10(-8) M ASX for CD3+CD25+ (SI = 0.79 +/- 0.04, P = 0.001) and 10(-7) M GB + 10(-7) M ASX for CD3+HLA-DR+ (SI = 0.82 +/- 0.05, P = 0.004). In conclusion, suppression of T cell activation below fully stimulated values by GB, ASX, and their combinations was comparable and for some combinations better than that mediated by CTZ and AZE. These results suggest that ASX and GB may have application as novel antiasthmatic formulations.

Publication Types:

- Comparative Study

PMID: 14978350 [PubMed - indexed for MEDLINE]

Additional Areas of Research: Asthma

Eur J Nutr. 2010 Apr 2. [Epub ahead of print]

Astaxanthin addition improves human neutrophils function: in vitro study.

Macedo RC, Bolin AP, Marin DP, Otton R.

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Tatuapé, São Paulo, SP, CEP 03342-000, Brazil.

Abstract

PURPOSE: The aim of the present study was to evaluate the in vitro effect of carotenoid astaxanthin (ASTA) on the phagocytic and microbicidal capacities, cytokine release, and reactive oxygen species production in human neutrophils.
METHODS: The following parameters were evaluated: cytotoxic effect of ASTA on human neutrophils viability, phagocytic and microbicidal capacities of neutrophils by using Candida albicans assay, intracellular calcium mobilization (Fura 2-AM fluorescent probe), superoxide anion (lucigenin and DHE probes), hydrogen peroxide (H(2)O(2), phenol red), and nitric oxide (NO.) (Griess reagent) production, activities of antioxidant enzymes (total/Mn-SOD, CAT, GPx, and GR), oxidative damages in biomolecules (TBARS assay and carbonyl groups), and cytokine (IL-6 and TNF-alpha) release.
RESULTS: Astaxanthin significantly improves neutrophil phagocytic and microbicidal capacity, and increases the intracellular calcium concentration and NO. production. Both functional parameters were accompanied by a decrease in superoxide anion and hydrogen peroxide and IL-6 and TNF-alpha production. Oxidative damages in lipids and proteins were significantly decreased after ASTA-treatment.
CONCLUSIONS: Taken together our results are supportive to a beneficial effect of astaxanthin-treatment on human neutrophils function as demonstrated by increased phagocytic and fungicide capacity as well as by the reduced superoxide anion and hydrogen peroxide production, however, without affecting neutrophils capacity to kill C. albicans. This process appears to be mediated by calcium released from intracellular storages as well as nitric oxide production.

PMID: 20361333 [PubMed - as supplied by publisher]

Additional Areas of Research: Candida

Phytother Res. 2010 Jan;24(1):54-9.

Cytoprotective role of astaxanthin against glycated protein/iron chelate-induced toxicity in human umbilical vein endothelial cells.

Nishigaki I, Rajendran P, Venugopal R, Ekambaram G, Sakthisekaran D, Nishigaki Y.

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Abstract

Astaxanthin (ASX), a red carotenoid pigment with no pro-vitamin A activity, is a biological antioxidant that occurs naturally in a wide variety of plants, algae and seafoods. This study investigated whether ASX could inhibit glycated protein/iron chelate-induced toxicity in human umbilical-vein endothelial cells (HUVEC) by interfering with ROS generation in these cells. Glycated fetal bovine serum (GFBS) was prepared by incubating fetal bovine serum (FBS) with high-concentration glucose. Stimulation of cultured HUVECs with 50 mm 1 mL of GFBS significantly enhanced lipid peroxidation and decreased antioxidant enzyme activities and levels of phase II enzymes. However, preincubation of the cultures with ASX resulted in a marked decrease in the level of lipid peroxide (LPO) and an increase in the levels of antioxidant enzymes in an ASX concentration-dependent manner. These results demonstrate that ASX could inhibit LPO formation and enhance the antioxidant enzyme status in GFBS/iron chelate-exposed endothelial cells by suppressing ROS generation, thereby limiting the effects of the AGE-RAGE interaction. The results indicate that ASX could have a beneficial role against glycated protein/iron chelate-induced toxicity by preventing lipid and protein oxidation and increasing the activity of antioxidant enzymes.

PMID: 19548280 [PubMed - indexed for MEDLINE]

Food Chem Toxicol. 2010 Jun;48(6):1741-5. Epub 2010 Apr 9.

Astaxanthin improves the proliferative capacity as well as the osteogenic and adipogenic differentiation potential in neural stem cells.

Kim JH, Nam SW, Kim BW, Kim WJ, Choi YH.

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Abstract

In the present study, the effect of astaxanthin on improvement of the proliferative capacity as well as the osteogenic and adipogenic differentiation potential in neural stem cells (NSCs) was evaluated. Treatment of astaxanthin-induced actives cell growth in a dose-dependent and time-dependent manner. Results from a clonogenic assay clearly indicated that astaxanthin can actively stimulate proliferation of NSCs. Astaxanthin-induced improvement in the proliferative capacity of NSCs resulted in overexpression of several proliferation-related proteins. Astaxanthin-induced activation of PI3K and its downstream mediators, p-MEK, p-ERK, and p-Stat3 in NSCs resulted in subsequent induction of expression of proliferation-related transcription factors (Rex1, CDK1, and CDK2) and stemness genes (OCT4, SOX2, Nanog, and KLF4). Astaxanthin also improved the osteogenic and adipogenic differentiation potential of NSCs. Astaxanthin-treated NSCs showed prominent calcium deposits and fat formation. These results were consistent with overexpression of osteogenesis-related genes (osteonectin, RXR, and osteopontin) and adipogenesis-related genes (AP and PPAR-gamma) after astaxanthin treatment. These findings clearly demonstrated that astaxanthin acts synergistically on the regulatory circuitry that controls proliferation and differentiation of NSCs.

PMID: 20385192 [PubMed - in process]

Additional Areas of Research: Neural Stem Cells

Eur J Pharm Sci. 2003 Jul;19(4):299-304.

Oral bioavailability of the antioxidant astaxanthin in humans is enhanced by incorporation of lipid based formulations.

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Astaxanthin is a carotenoid with antioxidant properties, synthesised by plants and algae, and distributed in marine seafood. Astaxanthin is also available as a food supplement, but, like other carotenoids, is a very lipophilic compound and has low oral bioavailability. However, bioavailability can be enhanced in the presence of fat. There is not much information in the literature about the pharmacokinetics of oral astaxanthin in humans. In this open parallel study, healthy male volunteers received a single dose of 40 mg astaxanthin, as lipid based formulations or as a commercially available food supplement, followed by blood sampling for further analysis of plasma concentrations. Pharmacokinetic parameters were calculated to evaluate the extent and rate of absorption from each formulation. The elimination half-life was 15.9+/-5.3 h (n=32), and showed a mono-phasic curve. Three lipid based formulations: long-chain triglyceride (palm oil) and polysorbate 80 (formulation A), glycerol mono- and dioleate and polysorbate 80 (formulation B), and glycerol mono- and dioleate, polysorbate 80 and sorbitan monooleate (formulation C), all showed enhanced bioavailability, ranging from 1.7 to 3.7 times that of the reference formulation. The highest bioavailability was observed with formulation B, containing a high content of the hydrophilic synthetic surfactant polysorbate 80.

Publication Types:

- Comparative Study

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Additional Areas of Research: Bioavailability

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On bioavailability and deposition of bent Z-isomers of astaxanthin

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Experiments have been performed in which rainbow trout (Oncorhynchus mykiss) were fed diets containing a mixture of the all-E, 9Z, and 13Z geometrical isomers of astaxanthin or three male middle-aged human subjects were administered a single dose containing a similar astaxanthin isomer mixture. In rainbow trout, selective accumulation of all-E-astaxanthin was observed in tissues and blood plasma, and of 13Z-astaxanthin in the liver. In human blood plasma, 13Z-astaxanthin appeared to accumulate, and the distribution of the astaxanthin E/Z isomers remained constant in the mixed chylomicron and very low density (VLDL), and low density (LDL) and high density (HDL) lipoprotein fractions. In conclusion, more attention than assumed in the past must be paid to the E/Z configuration of xanthophylls when bioavailability and functional aspects are concerned in different species.

Additional Areas of Research: Bioavailability

J Nutr Biochem. 2000 Oct;11(10):482-90.

Plasma appearance and distribution of astaxanthin E/Z and R/S isomers in plasma lipoproteins of men after single dose administration of astaxanthin.

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Appearance, pharmacokinetics, and distribution of astaxanthin E/Z and R/S isomers in plasma and lipoprotein fractions were studied in 3 middle-aged male volunteers (37-43 years) after ingestion of a single meal containing a 100 mg dose of astaxanthin. The astaxanthin source consisted of 74% all-E-, 9% 9Z-, 17% 13Z-astaxanthin (3R,3'R-, 3R,3'S; meso-, and 3S,3'S-astaxanthin in a 1:2:1 ratio). The plasma astaxanthin concentration--time curves were measured during 72 hr. Maximum levels of astaxanthin (1.3 +/- 0.1 mg/L) were reached 6.7 +/- 1.2 hr after administration, and the plasma astaxanthin elimination half-life was 21 +/- 11 hr. 13Z-Astaxanthin accumulated selectively, whereas the 3 and 3'R/S astaxanthin distribution was similar to that of the experimental meal. Astaxanthin was present mainly in very low-density lipoproteins containing chylomicrons (VLDL/CM; 36-64% of total astaxanthin), whereas low-density lipoprotein (LDL) and high-density lipoprotein (HDL) contained 29% and 24% of total astaxanthin, respectively. The astaxanthin isomer distribution in plasma, VLDL/CM, LDL, and HDL was not affected by time. The results indicate that a selective process increases the relative proportion of astaxanthin Z-isomers compared to the all-E-astaxanthin during blood uptake and that astaxanthin E/Z isomers have similar pharmacokinetics.

PMID: 11120445 [PubMed]

Additional Areas of Research: Bioavailability

Editors' Note: A complete Safety Profile for BioAstin® Natural Astaxanthin, a trademarked Astaxanthin product from Haematococcus Pluvialis microalgae is available at www.cyanotech.com

Food Chem Toxicol. 2008 Sep;46(9):3030-6. Epub 2008 Jun 10.

Safety assessment of astaxanthin-rich microalgae biomass: Acute and subchronic toxicity studies in rats.

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Astaxanthin, a natural nutritional component, is marketed as a dietary supplement around the world. The primary commercial source for astaxanthin is Haematococcus pluvialis (microalgae). The objective of the present study was to investigate the acute and subchronic toxicity of an astaxanthin-rich biomass of H. pluvialis (AstaCarox). The oral LD(50) of the biomass in rats was greater than 12g/kg body weight. In the subchronic study, Wistar rats (10/sex/group) were fed diets containing 0%, 1%, 5% and 20% of the biomass (weight/weight) for 90 days. trans-Astaxanthin was quantifiable in the plasma of the high-dose treated group only. Compared to the control group, no treatment-related biologically significant effects of astaxanthin were noted on body weight or body weight gain. Biomass feeding did not affect hematological parameters. In the high-dose group, slightly elevated alkaline phosphatase and changes in some urine parameters and an increase in kidney weight in both sexes were noted. Histopathology examinations did not reveal adverse effects except for a marginal increase in pigment in the straight proximal tubule of the kidney in 5/10 female rats treated with the high-dose. These changes were not considered as toxicologically significant. Although the rats in high-dose group received about 9% more fat, it is unlikely that this confounding factor significantly altered the outcome. The no-observed adverse-effect-levels (NOAEL) of the astaxanthin-rich biomass for male and female rats were determined as 14,161 and 17,076mg/kg body weight/day, or 465 and 557mg astaxanthin/kg/day, respectively, the highest dose tested.

Publication Types:

PMID: 18588938 [PubMed - indexed for MEDLINE]

Additional Areas of Research: Safety