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

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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-κB 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-κB activation and iNOS expression. Moreover, astaxanthin blocked nuclear translocation of NF-κB p65 subunit and I(κ)B(α) degradation, which correlated with its inhibitory effect on I(κ)B kinase (IKK) activity. These results suggest that astaxanthin, probably due to its antioxidant activity, inhibits the production of inflammatory mediators by blocking NF-κB activation and as a consequent suppression of IKK activity and I(κ)B-α degradation.

Publication Types:

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

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

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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.

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Anti-Inflammatory
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+/-.10 microM, 28.76+/-.48 microM, 9.79+/-.50 microM and 8.09+/-.99 microM, respectively. CpCpx and AcylCpCpx show greater NO radical scavenging than their parent compounds, curcumin and acetylcumcumin, 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+/-.50 microM.

Publication Types:

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

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Anti-Inflammatory
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.
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

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EFFECT OF AN ASTAXANTHIN-CONTAINING PRODUCT ON CARPAL TUNNEL SYNDROME
Nir, Y., Spiller, G., Multz, C.
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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.
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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

Anti-Inflammatory
Effect of Astaxanthin on Muscular Atrophy

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 sarcoplasmatic 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 mitochondria, 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.
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 sarcopenia. We tested the hypothesis that the long term dietary antioxidant (astaxanthin) intakes attenuate sarcopenia. 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 L and 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 tbcæ levels. There were no effects of Ax supplementation on calpain 1 and 2, UBC3B, CuZn SOD and nitrotyrosine levels in both soleus and tibialis anterior muscles. Our 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
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.

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

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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.

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