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

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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]

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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 antioxidantsexploited 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]
Biologic activity of carotenoids related to distinct membrane physicochemical interactions.

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

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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]
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:

PMID: 17685090 [PubMed - indexed for MEDLINE]
Astraxanthin vs placebo on arterial stiffness, oxidative stress and inflammation in renal transplant patients (Xanthin): a randomised controlled trial.

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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 astraxanthin 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 astraxanthin 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 astraxanthin 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 (Alx), 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 astraxanthin 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.

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PMCID: PMC2666668

Cardioprotective
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
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. Copyright 2008 S. Karger AG, Basel.

PMID: 18477858 [PubMed - indexed for MEDLINE]
Eulipidemic effects of berberine administered alone or in combination with other natural cholesterol-lowering agents. A single-blind clinical investigation.

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


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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]
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]
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; \( t=16/4 \) 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]
Seven day oral supplementation with Cardax (disodium disuccinate astaxanthin) provides significant cardioprotection and reduces oxidative stress in rats.

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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]
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]
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]
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]
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]
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]
Antihypertensive and neuroprotective effects of astaxanthin in experimental animals.

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

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

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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]
Inhibition of low-density lipoprotein oxidation by astaxanthin.


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

[Article in Russian]

Kukharchuk VV, Shumaev KB, Dmitrovskii AA, Cherniad'eva IF, Bykhovskii VIa.

PMID: 9162235 [PubMed - indexed for MEDLINE]
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.
Differential effects of carotenoids on lipid peroxidation due to membrane interactions: X-ray diffraction analysis

Hyesun P. McNulty a,*, Jungsoo Byun a, Samuel F. Lockwood b, 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.

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


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

Gross GJ, Lockwood SF.

Department of Pharmacology and Toxicology, Medical College of Wisconsin, Milwaukee, WI, USA.

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

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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
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.
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.
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
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
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.
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.
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.

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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.
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.

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

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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]
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.

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

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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.

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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.
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.

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