# ASTAXANTHIN IN INFLAMMATORY CONDITIONS

## ABSTRCTS – SCIENTIFIC STUDIES

*COMPILED BY*

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**Astaxanthin:**

Astaxanthin is one of a group of natural pigments known as carotenoids. In nature, carotenoids are produced principally by plants and microalgae. Carotenoids are molecules are associated with many of the colors that you see in leaves, flowers and fruit. They are one of the most abundant molecules in the world and give nature its wide variety of colors. Carotenoids have a long structure called the polyene system and may also have ring groups at one or either end. The differences in the polyene and ring structures are what vary the carotenoids and their corresponding colors due to different light absorbencies.

Astaxanthin is a natural carotenoid pigment red in colour. This xanthophyll is a fat soluble nutrient, which is a potential antioxidant more powerful than other antioxidants like betacarotene, Vit.E and Vit. C.

Astaxanthin gives salmon, shrimp, crustacean species and cooked lobsters their reddish pink color. Interestingly, when astaxanthin binds to different protein, it can appear green, yellow, blue or brown. When these "carotenoproteins" are denatured by cooking, astaxanthin is released and the red color becomes apparent again.

Astaxanthin has demonstrated powerful antioxidant activity and other beneficial properties for human health. Studies suggest that astaxanthin function in synergy with vitamin E and other antioxidants.

Through its antioxidant properties, astaxanthin helps to

- quenches singlet oxygen
- enhances the immune system
- protects against cancer of oral cavity, bladder, uterus, cervix and breast
- Protects against cardiovascular diseases
- Prevents certain photosensitivity disorders.
- improves antioxidant actions in tissues
- Suppresses inflammation
- Improves tissue recovery from oxidative damage

These unique properties open very promising possibilities for nutraceutical and pharmaceutical application of astaxanthin in humans.

We produce astaxanthin from the alga Haematococcus pluvialis. Commercial production of astaxanthin from the microalga Haematococcus pluvialis is a growing business worldwide, primarily due to the rapid growth of this microorganism and its astaxanthin content.

**Inflammatory Disorders and Arthritis.**

Inflammation is a complex process with varied causes and response mechanisms. Inflammation sets the stage for chronic and age related disorders and many scientific studies have confirmed this. As humans grow older, [illegible]emic inflammation can cause degenerative effects throughout the body (McCarty MF, 1999 and Brod SA., 2000).

Inflammation begins with the release of inflammatory markers like C-reactive protein, interleukin-1B (IL-1B), interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-alpha) as well as inflammatory mediators like nitric oxide and prostaglandin E2, which are synthesized by nitric oxide synthase and the cox enzymes.

In inflammation-related conditions, toxic Reactive Oxygen Species (ROS) are released at the site of inflammation. These, plus increased concentrations of [illegible]trophiles at the site of inflammation, create a pro-oxidative balance that leads to lower levels of antioxidant vitamins and increased levels of markers of oxidative stress and lipid peroxidation. Similarly, ROS have been attributed an aggravating role in the inflammation that accompanies asthma (Greene, L. 1995) and exercise-induced muscle damage (Dekkers, J. et al. (1996). Furthermore, oxidants have been directly linked to the stimulation of inflammation genes in endothelial cells (Aw, T.Y., 1999)

Studies have also indicated that these infirmities of aging may be prevented or reversed by correcting these chronic inflammatory conditions. [illegible]hritis is an inflammatory disorder which involves progressive degeneration of normal joints. It is also believed that the immune system and genetic disposition are known to play a role in rheumatoid arthritis. In arthritic conditions, over time, there is progressive deformity of the affected joints and arthritis can occur in the joints of our writs, shoulders, elbows, fingers, knees and hips – accompanied by pain and muscle spasm.

Conventional medical treatment of arthritis is symptomatic and does not help the body repair the joint. Nutritional therapy may be best for arthritis. Supplementing carotenoids can be used therapeutically to manage rheumatoid arthritis

**Astaxanthin in Inflammation:**

Scientific studies have confirmed the fact that free radicals are the underlying cause of any health problem. Free radicals seem to be the cause of inflammation in the Joints and cause pain in the joints. With rheumatoid arthritis it is an immune rejection in joints and the first immune response of the body is to generate free radicals. Nutritional therapy with astaxanthin is an effective way in controlling inflammatory conditions. Studies have shown that astaxanthin as an antioxidant pigment contains specific anti-inflammatory properties and through this antioxidant property, astaxanthin seems to be more effective in these conditions as this carotenoid help in neutralizing the free radicals and minimize the oxidative damage in the joints.

Astaxanthin is showing benefits as an anti-inflammatory (Shimizu, N. et al 1996) by inhibiting the production of the pro-inflammatory mediators (Lee, S.J., 2003). Astaxanthin appears to work through multiple pathways to combat inflammation throughout the entire body. It does act as a mild cox-1 and cox-2 inhibitor. It also suppresses the other inflammatory agents in the body such as prostaglandin E2, nitric oxide, IL-1B, TNF-alpha and C-reactive protein (CRP) – the proinflammatory mediators, which promote inflammatory responses. Exposure to outer bacterial toxins stimulates cellular responses and releases these proinflammatory mediators (Ohgami K, et al, 2003).

A 2003 rat study found that astaxanthin inhibits iNOS enzyme activity, which decreases production of nitric oxide as well as prostaglandin E2 and TNF-alpha (Ohgami K, et al, 2003). Astaxanthin supplementation at 12mg / day seems to have a significant drop in the CRP level compared to the placebo group in an eight-week, double-blind, placebo-controlled human clinical trial (Spiller GA, et al). CRP is one of the acute-phase proteins that increase during systemic inflammation.

Astaxanthin was found to reduce induced swelling of rat paw, that vitamin E did not reduce (Kurashige M et. Al 1990). More recently, dietary astaxanthin was found to help fight symptoms of ulcer disease from Helicobacter pylori. Astaxanthin was found to reduce the symptoms of gastric inflammation and was also associated with shifts in the inflammation response (Bennedesen, M et al. 1999 and Wang, X et al. 2000).

Other research (Cyanotech press release October 2002) shows astaxanthin's utility with a range of inflammatory conditions including rheumatoid arthritis, carpal tunnel syndrome, tendonitis, joint and muscle soreness after exercise, and as an internal sunblock — another inflammatory condition because sunburn is an inflammation of the body's largest organ, the skin. Its effects are typically seen in two to four weeks. Astaxanthin seems to be effective in these conditions of Carpel Tunnel Syndrome, rheumatoid arthritis and joint conditions, because of its antioxidant property, since free radicals seem to be the major factor that affects our immune system. These studies indicates that the sufferers from Carpel Tunnel syndrome reported decreased writs pain while those with Rheumatoid Arthritis reported less daytime pain.

The anti-inflammatory activity observed in the scientific studies was attributed to antioxidant effect and oxygen scavenging activity of astaxanthin (Lee, S.J et al. 2003, Krinsky, N.I, 1989, Palozza, P. & Krinsky, N.I. 1992, Naguib, Y.M. 2000). Astaxanthin has been shown to be 550 times stronger than vitamin E in singlet oxygen quenching (Shimizu, N. etal 1996). Thus astaxanthin has been found helpful in inflammatory disorders and in relieving the symptoms of rheumatoid arthritis.

**References:**

1. Aw, T.Y. 1999 Molecular and cellular responses to oxidative stress and changes in oxidation-reduction imbalance in the intestine. *Am. J. Clin. Nutr. 70, 557–565* Abstract / Full Text
2. Bennedsen M, Wang X, Willen R, Wadstrom T, Andersen LP. 1999 Treatment of H. pylori infected mice with antioxidant astaxanthin reduces gastric inflammation, bacterial load and modulates cytokine release by splenocytes. *Immunol. Lett. 70, 185–189.* Abstract
3. Brod SA. 2000 Unregulated inflammation shortens human functional longevity. *Inflamm Res. 49(11):561-70.* Abstract
4. Cyanotech Press Release, 2002.
5. Dekkers JC, van Doornen LJ, Kemper HC. 1996 The role of antioxidant vitamins and enzymes in the prevention of exercise-induced muscle damage. *Sports Med. 21, 213–238* Abstract
6. Greene, L. 1995 Asthma and oxidant stress: nutritional, environmental, and genetic risk factors. *J. Am. Coll. Nutr. 14, 317–324* Abstract
7. Kazuhiro Ohgami, Kenji Shiratori, Satoshi Kotake, Tomomi Nishida, Nobuhisa Mizuki, Kazunaga Yazawa, and Shigeaki Ohno. 2003 Effects of astaxanthin on lipopolysaccharide-induced inflammation in vitro and in vivo *Ophthamol Visual Sci 44(4): 2694-2701.* Abstract/Full Text
8. Krinsky N I. 1989. Antioxidant function of carotenoids. Free Radic Biol Med. **7**:617–635. Abstract
9. Kurashige M, Okimasu E, Inoue M, Utsumi K. 1990 Inhibition of oxidative injury of biological membranes by astaxanthin. *Physiol Chem Physics Med NMR* **22***:27–38.* Abstract
10. Lee SJ, Bai SK, Lee KS, Namkoong S, Na HJ, Ha KS, Han JA, Yim SV, Chang K, Kwon YG, Lee SK, Kim YM. 2003 Astaxanthin inhibits nitric oxide production and inflammatory gene expression by suppressing IkB kinase-dependent NF-kB activation. *Mol Cells 16(1);97-105.* Abstract
11. McCarty MF. 1999. Interleukin-6 as a central mediator of cardiovascular risk associated with chronic inflammation, smoking, diabetes, and visceral obesity: down-regulation with essential fatty acids, ethanol and pentoxifylline. *Med Hypotheses. 52(5):465-77* Abstract
12. Naguib YM. 2000 Antioxidant activities of astaxanthin and related carotenoids. *J Agric Food Chem. 48(4):1150-4.* Abstract
13. Palozza P, Krinsky N I. 1992. Astaxanthin and canthaxanthin are potent antioxidants in a membrane model. *Arch Biochem Biophys.* **297***:291–295.* Abstract
14. Shimizu, N. et al. 1996 Carotenoids as single oxygen quenchers in marine organisms. *Fisheries Sci 62;134-7.*
15. Spiller GA, et al. Effect of daily use of natural astaxanthin on C-reactive protein. Unpublished.
16. Xin Wang, Roger Willén, and Torkel Wadström 2000 Astaxanthin-rich algal meal and vitamin C inhibit Helicobacter pylori infections in BALB/cA mice. *Antimicrob Agents Chemother 44:2452-7.* Full Text

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

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

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

Vascular System Research Center and Department of Molecular and Cellular Biochemistry, Kangwon National University Biology, Chunchon 200-701, Korea. Astaxanthin, a carotenoid without vitamin A activity, has shown anti-oxidant and anti-inflammatory activities; however, its molecular action and mechanism have not been elucidated. We examined in vitro and in vivo regulatory function of astaxanthin on production of nitric oxide (NO) and prostaglandin E2 (PGE2) as well as expression of inducible NO synthase (iNOS), cyclooxygenase-2, tumor necrosis factor-alpha (TNF-alpha), and interleukin-1beta (IL-1beta). Astaxanthin inhibited the expression or formation production of these proinflammatory mediators and cytokines in both lipopolysaccharide (LPS)-stimulated RAW264.7 cells and primary macrophages. Astaxanthin also suppressed the serum levels of NO, PGE2, TNF-alpha, and IL-1beta in LPS-administrated mice, and inhibited NF-kappaB activation as well as iNOS promoter activity in RAW264.7 cells stimulated with LPS. This compound directly inhibited the intracellular accumulation of reactive oxygen species in LPS-stimulated RAW264.7 cells as well as H2O2-induced NF-kappaB activation and iNOS expression. Moreover, astaxanthin blocked nuclear translocation of NF-kappaB p65 subunit and I(kappa)B(alpha) degradation, which correlated with its inhibitory effect on I(kappa)B kinase (IKK) activity. These results suggest that astaxanthin, probably due to its antioxidant activity, inhibits the production of inflammatory mediators by blocking NF-kappaB activation and as a consequent suppression of IKK activity and I(kappa)B-alpha degradation.

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

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

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.**

Guerin M, Huntley ME, Olaizola M.

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

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.

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

Aoi W, Naito Y, Sakuma K, Kuchide M, Tokuda H, Maoka T, Toyokuni S, Oka S, Yasuhara M, Yoshikawa T.
Department of Medicine, Kyoto Prefectural University of Medicine, Kyoto, 602-0841.

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

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

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

Wang X, Willen R, Wadstrom T. Department of Infectious Diseases and Medical Microbiology, University of Lund, Sweden.

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

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

**Antioxidant activities of astaxanthin and related carotenoids.**
Naguib YM. Phytochem Technologies, Chelmsford, MA 01824, USA.

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

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

**Unregulated inflammation shortens human functional longevity.**
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***Inflamm Res. 2000 Nov;49(11):561-70.***

Systemic inflammation, represented in large part by the production of pro-inflammatory cytokines, is the response of humans to the assault of the non-self on the organism. Three distinct types of human ailments - namely autoimmunity, presenile dementia (Alzheimer's disease), or atherosclerosis - are initiated or worsened by systemic inflammation. Autoimmunity is unregulated hyper immunity to organ-specific proteins, inducing rapid turnover of antigen-specific T cells of the acquired immune system with ultimate exhaustion and loss of acquired immunity IL-2 and IFN-gamma production and proliferative decline, conforming to the limited capacity of clonal division (Hayflick phenonmenon). In Alzheimer's disease (AD), the primary degenerative process of amyloid-beta (AJ3) protein precedes a cascade of events that ultimately leads to a local "brain inflammatory response". Unregulated systemic immune processes are secondary but important as a driving-force role in AD pathogenesis. Atherosclerosis, an underlying cause of myocardial infarction, stroke, and other cardiovascular diseases, consists of focal plaques characterized by cholesterol deposition, fibrosis, and inflammation. The presence of activated T lymphocytes and macrophages indicate a local immunologic activation in the atherosclerotic plaque that may be secondary to unregulated pro-inflammatory cytokines too. The premature hyper immunity of autoimmunity, the local "brain inflammatory response" to A/3 protein in AD, and the immune response to fatty changes in vessels in atherosclerosis all signal the critical importance of unregulated systemic inflammation to common neurological and cardiovascular disease that shortens the nominal longevity of humans.

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

Bennedsen M, Wang X, Willen R, Wadstrom T, Andersen LP.

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

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

**Molecular and cellular responses to oxidative stress and changes in oxidation-reduction imbalance in the intestine**

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*American Journal of Clinical Nutrition, Vol. 70, No. 4, 557-565, October 1999*

Recently, it has become increasingly apparent that oxidants, in addition to being agents of cytotoxicity, can play an important role in mediating specific cell responses and expression of genes involved in degenerative pathophysiologic states, such as inflammation and cancer. In particular, nuclear transcription factor B (NF-B), a multisubunit transcription factor, has been implicated in the transcriptional up-regulation of inflammatory genes in response to oxidants or changes in cellular oxidation-reduction status. This paper provides an overview of the cellular responses to oxidative stress and oxidation-reduction imbalance and the role of NF-B in these responses and summarizes the current strategies used to study NF-B activation and nuclear translocation, particularly in relation to dietary oxidant-mediated pathophysiology of the intestine

**Interleukin-6 as a central mediator of cardiovascular risk associated with chronic inflammation, smoking, diabetes, and visceral obesity: down-regulation with essential fatty acids, ethanol and pentoxifylline.**

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***Med Hypotheses. 1999 May;52(5):465-77. Links***

Increased plasma levels of fibrinogen and C-reactive protein (CRP), as well as leukocytosis, are now established as risk factors for the thromboembolic complications of vascular disease. Chronic inflammation or infection associated with an acute-phase response--notably, periodontal disease and smoking-induced lung damage--are likewise known to increase cardiovascular risk. A common etiologic factor in these conditions may be interleukin-6 (IL-6), acting on hepatocytes to induce acute-phase reactants that increase blood viscosity and promote thrombus formation. Recent evidence that hypertrophied adipocytes release IL-6, and that hyperglycemia evokes IL-6 production by endothelium, may explain why plasma fibrinogen is increased in visceral obesity and poorly controlled diabetes. IL-6 is released by a range of tissues in response to stimulation by the monocyte-derived cytokines interleukin-1 and tumor necrosis factor; by suppressing production of these cytokines, fish oil, alpha-linolenic acid, and pentoxifylline can reduce IL-6 synthesis. Moderate ethanol consumption, as well as sex-hormone replacement, also appear to inhibit IL-6 production or activity. These practical protective measures may be of particular value to patients with pre-existing atheroma and elevated plasma levels of acute-phase reactants. Since IL-6 plays a crucial physiological role in osteoclast generation and activation, these measures may also aid preservation of bone density.

**The role of antioxidant vitamins and enzymes in the prevention of exercise-induced muscle damage.**

Dekkers JC, van Doornen LJ, Kemper HC.
Department of Health Sciences in Relation to Human Movement, Vrije Universiteit, Amsterdam, Netherlands.

***Sports Med. 1996 Mar;21(3):213-38.***

A growing amount of evidence indicates that free radicals play an important role as mediators of skeletal muscle damage and inflammation after strenuous exercise. It has been postulated that the generation of oxygen free radicals is increased during exercise as a result of increases in mitochondrial oxygen consumption and electron transport flux, inducing lipid peroxidation. The literature suggests that dietary antioxidants are able to detoxify the peroxides produced during exercise, which could otherwise result in lipid peroxidation, and that they are capable of scavenging peroxyl radicals and therefore may prevent muscle damage. Endogenous antioxidant enzymes also play a protective role in the process of lipid peroxidation. The studies reviewed (rodent and human) show significant increases of malondialdehyde (a product of lipid peroxidation) after exercise to exhaustion, and also favourable changes in plasma antioxidant levels and in antioxidant enzyme activity. In trained individuals and trained rats, the antioxidant enzyme activity increases markedly. In this way, the increased oxidative stress induced by exercise is compromised by increased antioxidant activity, preventing lipid peroxidation. Human studies have shown that dietary supplementation with antioxidant vitamins has favourable effects on lipid peroxidation after exercise. Although several points of discussion still exist, the question whether antioxidant vitamins and antioxidant enzymes play a protective role in exercise-induced muscle damage can be answered affirmatively. The human studies reviewed indicate that antioxidant vitamin supplementation can be recommended to individuals performing regular heavy exercise. Moreover, trained individuals have an advantage compared with untrained individuals, as training results in increased activity of several major antioxidant enzymes and overall antioxidant status. However, future studies are needed in order to be able to give more specific information and recommendations on this topic.

**Asthma and oxidant stress: nutritional, environmental, and genetic risk factors**

L. S. Greene
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***Journal of the American College of Nutrition, 1995 Vol 14, Issue 4 317-324,***

A considerable body of evidence suggests that oxidant stress results in inflammation and tissue damage in the respiratory system, and later in immune damage, and that individuals with lowered cellular reducing capacity are at increased risk to develop asthma. Reducing capacity in the erythrocyte is generated through the pentose phosphate pathway and this pathway also generates a major portion of the reducing capacity in all cells of the body. Therefore, dietary, environmental, and genetic factors which diminish cellular reducing capacity will increase tissue vulnerability to oxidant stress and are likely to increase asthma risk. Dietary selenium deficiency lowers red cell glutathione peroxidase activity and is associated with an increased risk for asthma, and low dietary intakes of vitamins C and E also appear to increase asthma risk. High body iron stores increase free radical production and may also elevate asthma risk. Environmental lead exposure depresses the activities of a several enzyme systems that influence cellular reducing capacity (glucose-6-phosphate dehydrogenase, NAD synthetase, glutathione peroxidase, superoxide dismutase, catalase) and consequently may increase asthma risk. Genetically-determined low activity of glucose-6-phosphate dehydrogenase lowers cellular reducing capacity and may also heighten asthma risk. Simple dietary and environmental interventions may significantly reduce oxidant stress and prevent or minimize the development of asthmatic symptoms and should prove to be a cost effective approach to asthma management in addition to current pharmacological strategies.

**Astaxanthin and canthaxanthin are potent antioxidants in a membrane model.**

Palozza P, Krinsky NI.
Department of Biochemistry, Tufts University School of Medicine, Boston, Massachusetts 02111-1837.

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

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

**Inhibition of oxidative injury of biological membranes by astaxanthin.**

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

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

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

**Antioxidant functions of carotenoids.**

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***Free Radic Biol Med. 1989;7(6):617-35.***

Carotenoid pigments, including hydrocarbons such as beta-carotene or xanthophylls such as lutein and zeaxanthin, are very widely distributed in nature, where they play an important role in protecting cells and organisms against the harmful effects of light, air, and sensitizer pigments. This process has been demonstrated in bacteria, algae, plants, animals, and even in humans in the light-sensitive disease, erythropoietic protoporphyria. The primary mechanism of action of this phenomenon appears to be the ability of carotenoids to quench excited sensitizer molecules as well as quench 1O2. In addition to this protection, and potentially of even greater biological importance, is the fact that carotenoids can also serve as antioxidants under conditions other than photosensitization. This review presents the data available indicating the extent of this important function. Antioxidant action can be documented in both enzymic and nonenzymic systems, and has been reported in subcellular, cellular, and animal studies. In fact, the many reports indicating that carotenoids may possess some anticarcinogenic properties may well be related to their ability to interact with and quench various radical species that can be generated within cells.