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Novel Antioxidant

Astaxanthin leads the next generation
of free radical fighters

Nutrients that Sustain the Brain

Enzymes for Pain Relief

Does Fiber Promote Colon Cancer?

Also Inside: 3 New Columns Debut

.1 CEU: BARLEY GRASS

Pioneering Astaxanthin

During the late nineties, antioxidant research surged, particularly on carotenoids—that fat-soluble group of pigments widely distributed in plants and animals.

Carotenoids have demonstrable antioxidant abilities and are thought to be important in helping to prevent numerous diseases. Some of the more exciting new research is being done on age-related macular degeneration.

As a member of the carotenoid group xanthophylls, astaxanthin possesses oxygen in its chemical structure. Other xanthophylls include canthaxanthin, cryptoxanthin, lutein, and zeaxanthin. Some of the better-known carotenoids of other groups are beta-carotene (present in carrots), lycopene (in tomatoes), and lutein (in spinach). Unlike beta-carotene, astaxanthin lacks pro-vitamin A activity.¹

My work as a research scientist and chemist has involved me with much in vitro research. I became interested in astaxanthin in 1997 when I found that it possesses antioxidant activity comparable to many lipid-soluble antioxidants.

Astaxanthin is a well-known carotenoid marketed as a dietary supplement in Japan and Europe since the late 1990s. It is naturally derived for commercial use from the microalgae *Haematococcus pluralis*, though most often a synthetic version is used. In April 2000, one of my laboratory research studies was published in the *Journal of*

Agricultural and Food Chemistry. In our lab, my team and I developed a new fluorometric assay for measuring antioxidant activity. We compared the relative antioxidant strength of astaxanthin to fellow carotenoids alpha-

carotene, beta-carotene, lutein, and lycopene, as well as to vitamin E, which is considered one of the strongest antioxidants and thus a good comparative measure. In three different

assays, astaxanthin showed the highest antioxidant activity toward peroxy radicals—a variety of damaging free radicals—in two trials and second to only vitamin E in the third.

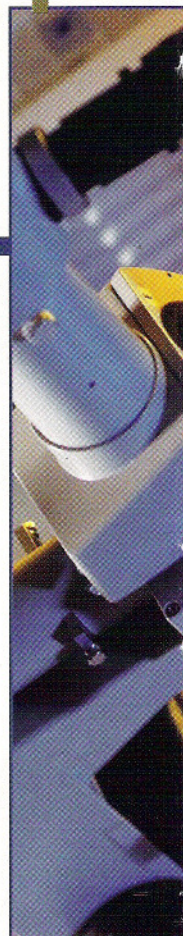
For example, one of our trials showed astaxanthin at 1.3 on our rating scale, vitamin E at 0.9, alpha-carotene at 0.5, lutein and lycopene at 0.4, and beta-carotene at 0.2. In another assay, vitamin E scored highest at 1.3 compared to astaxanthin's 1.0 rating.³ Findings such as these validate the increased consumer interest in astaxanthin as a sound antioxidant dietary supplement.

Similar studies showing astaxanthin's antioxidant capabilities as equal to or greater than vitamin E have one fellow astaxanthin researcher referring to the carotenoid as the "super vitamin E."²

Stemming from astaxanthin's antioxidant actions are studies—mostly in vitro and animal—suggesting dietary supplement applications against cancer, ultraviolet damage to the skin and macula of the eye, and cardiovascular conditions. Anecdotal reports that are as-yet unconfirmed in the lab or in clinical trials speak of endurance boosts as well as benefits for repetitive motion conditions such as carpal tunnel syndrome.

Major Antioxidant Studies

Oxygen is essential for aerobic metabolism; a by-product of this process is formation of oxygen free radicals, which play a vital role in fighting infections and in other essential biochemical processes. However, if these radicals are left unchecked, they can attack and damage cells and



The carotenoid astaxanthin is perhaps best known as the agent that provides the pinkish-red color to farm-raised fish such as salmon. Recent research also shows it to be a potent antioxidant equal to or greater than lipid-soluble antioxidants such as vitamin E. Predominantly through its antioxidant effects, astaxanthin may enhance immune response, protect vision, and exert anti-cancer effects.

A leading researcher surveys the antioxidant frontier and reports on potential uses for this nutrient new to the U.S. market

BY YOUSRY NAGUIB, PH.D.

glet oxygen. In fact, one study shows the singlet oxygen-quenching ability decreasing in the following order: astaxanthin, canthaxanthin, beta-carotene, zeaxanthin, lutein, and synthetic vitamin E.⁴

Several studies have been conducted on the effects of carotenoids on radical-mediated lipid peroxidation in microsomes and in model membranes, a process implicated in aging, atherosclerosis, cancer, and other conditions. One in vitro study at Kyoto University in Japan found synthetic astaxanthin and canthaxanthin could retard peroxyl free radical-induced oxidation of an unsaturated fatty acid ester more efficiently than beta-carotene and zeaxanthin.⁵

A similar study showed natural astaxanthin is the most efficient antioxidant in retarding free radical-mediated oxidation of the omega-6 fatty acid linoleic acid, with the free radical-scavenging ability decreasing in the following order: astaxanthin, zeaxanthin, canthaxanthin, lutein, beta-carotene, and vitamin E. The study also reported that astaxanthin showed inhibitory activity 100 times greater than that of alpha-tocopherol on peroxyl radical-mediated lipid peroxidation of rat mitochondria.²

In a lab study conducted at Tufts University School of Medicine in Boston, astaxanthin provided greater protection than beta-carotene to rat liver microsomes undergoing free radical-initiated lipid peroxidation and was as effective as vitamin E.⁶ Furthermore, in vitamin E-deficient rats, synthetic astaxanthin protected mitochondria from damage caused by lipid peroxidation, and the antioxidant activity was greater than that of supplemental vitamin E.⁷ The latter study, conducted at Kochi Medical School in Japan, also found artificially induced inflammation of rat paws was significantly inhibited by astaxanthin.

Other Antioxidant Effects

Astaxanthin also has the ability to efficiently trap peroxyl radicals, thus inhibiting that pathway of lipid peroxidation and suppressing the deleterious effects of peroxyl

DNA, opening the door to the aging process and a host of various degenerative diseases including age-related eye diseases, Alzheimer's, arthritis, cancer, diabetes, heart disease, and inflammatory disorders. Antioxidants such as carotenoids and bioflavonoids help cells cope with oxidative stress by neutralizing free radicals and, for this reason, have also been linked to disease prevention.

Carotenoids are considered potential membrane antioxidants due to the way they react with oxygen free radicals and singlet oxygen—a nonradical pro-oxidant found in biological systems and capable of damaging proteins, lipids, and DNA. Astaxanthin attaches itself onto cell membranes and spans the cell membrane bilayer of fat and water where free radical attack first occurs. By doing so it inhibits the destruction of fatty acids and proteins in cell and mitochondrial membranes caused by fat peroxidation.

Astaxanthin is one of the more potent quenchers of sin-

ASTAXANTHIN

radicals. Therefore, astaxanthin is thought to enhance humoral immune responses in humans, protect against tumor formation and skin cancer, ameliorate degeneration of retinal photoreceptors, and protect the central nervous system.

► **HUMORAL IMMUNE RESPONSE:** Research demonstrates that astaxanthin protects against pathogens by promoting humoral immune responses. These involve antibodies that are secreted by B cells and circulate in bodily fluids. Such responses decline with age, often resulting in autoimmune diseases, frequent infections, and even cancer. In culture and animal tests, astaxanthin's enhancement of humoral immune responses suggests a potential role in older people by partially restoring specific antibody responses and maintaining the immune response at optimal levels.^{1,8}

► **ANTITUMOR ACTIVITY:** Astaxanthin's ability to enhance immune responses in mice has a corollary effect of exhibiting anti-tumor activity. Researchers at the University

of Minnesota fed mice 40 mcg astaxanthin/kg body weight per day. Those mice had significantly smaller tumors than controls when supplementation was started one and three weeks before tumor inoculation.⁹

Another mouse study, at Washington State University in Pullman, showed astaxanthin inhibits the growth of mammary tumors in mice by modulating tumor latency and exerting antioxidant effects. Mice were fed a diet containing 0, 0.1, or 0.4 percent astaxanthin, beta-carotene, or cantaxanthin. Three weeks later, all mice were inoculated with tumor cells. After 45 additional days, plasma concentrations of the carotenoids were undetectable in unsupplemented mice but pronounced in the supplemented group. In general, all three carotenoids decreased mammary tumor volume. Lipid peroxidation activity in tumors was lower in mice fed astaxanthin, which dose-dependently inhibited mammary tumor cell growth, and was most effective of the three carotenoids.¹⁰

ASTAXANTHIN is best known for its commercial use in the aquaculture industry. In its pure, synthetic form, fish farmers use it to provide the pinkish-red color to salmon, trout, and crustaceans such as crabs, krill, and shrimp. The ruddy pigmentation of the fish flesh brought about by astaxanthin is considered an important consumer criterion of quality. Wild fish acquire their characteristic salmon flesh color from astaxanthin found in the single-celled organisms they eat.

The fact that salmon cannot synthesize

Many carcinogens undergo detoxification by xenobiotic-metabolizing enzymes, which enhance the diversion of toxic by-products toward detoxification pathways.¹¹ Xenobiotics are chemicals that are foreign to the biological system and

Values Astaxanthin

astaxanthin and must find it in their diet to maintain pink-colored flesh—and can reproduce only if astaxanthin is present in their diets—are indications of astaxanthin's necessity in these animals.¹

Owing to the high demand for astaxanthin in animal feed, particularly aquaculture and poultry (for egg yolk color enhancement), astaxanthin is chemically synthesized on a large scale. The worldwide market is estimated at about \$185 million in 2000 and is growing rapidly.

Astaxanthin is found naturally in certain plants. The yeast *Phaffia rhodozyma* and the microalgae *Haematococcus pluvalis* are the only microorganisms able to biosynthesize astaxanthin in appreciable yields and have recently gained considerable interest as sources of natural astaxanthin. Among the natural sources, *H. pluvalis* contains the highest level of astaxanthin, which exists mainly as esters of various fatty acids.

Astaxanthin occurs in several different forms depending on its precise

molecular makeup. Many laboratory studies use synthetic astaxanthin. Although similar in action, one difference noted between the two forms is that natural astaxanthin tends to produce a higher pigmentation in rainbow trout compared to synthetic astaxanthin provided at the same dietary concentration.² Other nutrients contained in natural sources, as well as subtle chemical differences between the two forms, may also account for nonidentical activities.

—Y.N.

include naturally occurring compounds and drugs. Xenobiotic metabolism is the physical and chemical change that affects foreign substances in living organisms from uptake to excretion.¹² Astaxanthin has been shown to induce rat lung and kid-

ney xenobiotic-metabolizing enzymes.¹³

A recent animal study reports on the benefits of astaxanthin against *Helicobacter pylori*, which in humans is associated with chronic type B gastritis, peptic ulcer disease, and, more importantly, gastric carcinoma. In this

study, conducted at the University of Lund in Sweden, mice infected with *H. pylori* were given daily treatments for 10 days of either algal meal rich in astaxanthin of various potencies (10, 50, and 100 mg/kg body weight), 400 mg/kg vitamin C, or control ►

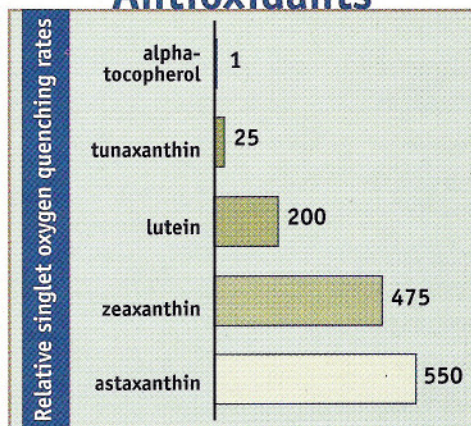
ASTAXANTHIN

meals. After one and 10 days post-treatment, both the astaxanthin and vitamin C groups showed significantly lower *H. pylori* colonization levels and lower inflammation scores than controls, with astaxanthin showing a dose-dependent response.¹⁴

▶ EYE HEALTH: Certain carotenoids have been shown to help protect the retina of the eye from oxidative damage.¹⁵ The lens of the eye focuses incoming light onto the photosensitive retina, which transmits visual signals to the brain. In the central area of the retina lies the macula, which has the highest density of photoreceptors that provide visual acuity. Oxidation, as from sunlight exposure, degrades membranes and likely leads to damage or destruction of photoreceptor cells.¹⁶

A recent U.S. rat study indicates astaxanthin is able to cross the blood-retinal barrier and exert antioxidant effects to ameliorate retinal injury by staving off light-induced oxidation and protecting photoreceptors from degeneration.¹⁷ The carotenoid pigments lutein and zeaxanthin, which concentrate in the macula, absorb blue light and quench singlet oxygen radicals.¹⁸ As previously mentioned, astaxanthin similarly has been shown to be an excellent quencher of singlet oxygen radicals.

Antioxidants



The photoreceptor cells are a constituent of the outer neuronal layer of the retina, which is a component of the central nervous system. These study results suggest astaxanthin may prevent and treat neuronal damage associated with age-related macular degeneration, and may also treat ischemic reperfusion injury, Alzheimer's disease, Parkinson's disease, spinal cord injuries, and other types of central nervous system injuries. However, studies have yet to be conducted to validate astaxanthin's effects on these conditions.

▶ CARDIOVASCULAR HEALTH: Cholesterol is a primary indicator of cardiovascular health. It is now established that the gauge of health comes not so much from total cholesterol levels as from the ratio of high-density lipoproteins (HDL, or "good" cho-

lesterol) to low-density lipoproteins (LDL, or "bad" cholesterol). A study at the University of Panama measured cholesterol levels of rats fed diets containing 1,000 parts per million beta-carotene, canthaxanthin, and astaxanthin, respectively, for 30 days. Those on astaxanthin and canthaxanthin showed significant increases in HDL.¹⁹

Toxicity of astaxanthin is not believed to be a problem, although toxicity and safety studies have only been conducted on the natural *Haematococcus pluvalis* algae and most of the scientific studies have used synthetic astaxanthin. The toxicity results on *H. pluvalis* were negative. A Japanese 13-week oral repeated dose rat study found *H. pluvalis* administration corresponding to 0.5, 1.5, and 5 percent astaxanthin showed no toxicological changes.²⁰

Most astaxanthin studies conducted thus far have been on animals or in laboratories. Although these preliminary results have been promising enough to ignite the astaxanthin supplements market, most researchers agree that larger, prospective human clinical trials are necessary to adequately evaluate the antioxidant and protective effects of astaxanthin in humans. ^{NSN}

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REFERENCES

1. Jyonouchi H, et al. Astaxanthin, a carotenoid without vitamin A activity, augments antibody responses in cultures including T helper cell clones and suboptimal doses of antigen. *J Nutr* 1995;125(10):2483-92.
2. Miki W. Biological functions and activities of animal carotenoids. *Pure Appl Chem* 1991;63:141.
3. Naguib YM. Antioxidant activities of astaxanthin and related carotenoids. *J Agric Food Chem* 2000 Apr;48(4):1150-4.
4. DiMascio P, et al. Carotenoids, tocopherols and thiols as biological singlet molecular oxygen quenchers. *Biochem Soc Transactions* 1990;18:1054.
5. Terao J. Antioxidant activity of beta-carotene and related carotenoids in solution. *Lipids* 1989;24:659.
6. Palozza R, Krinsky NI. Astaxanthin and canthaxanthin are potent antioxidants in a membrane model. *Arch Biochem Biophys* 1992 Sep;297:291-5.
7. Kurashige M, et al. Inhibition of oxidative injury of biological membranes by astaxanthin. *Physiol Chem Phys Med NMR* 1990;22(1):27-8.
8. Thompson I, et al. The effect of dietary vitamin A and astaxanthin on the immunocompetence of rainbow trout. *Aquaculture* 1995;133:91-102.
9. Jyonouchi H, et al. Antitumor activity of astaxanthin and its mode of action. *Nutr Cancer* 2000;36(1):59-65.
10. Chew BP, et al. A comparison of the anticancer activities of dietary beta-carotene, canthaxanthin and astaxanthin in mice in vivo. *Anticancer Res* 1999 May-Jun;19(3A):1849-53.
11. Gradellet S, et al. Modulation of aflatoxin B1 carcinogenicity, genotoxicity and metabolism in rat liver by dietary carotenoids: evidence for a protective effect of CYP1A inducers. *Cancer Lett* 1997;114(1-2):221-3.
12. Jewell C, O'Brien NM. Effect of dietary supplementation with carotenoids on xenobiotic metabolizing enzymes in the liver,

- lung, kidney and small intestine of the rat. *Br J Nutr* 1999 Mar;81(3):235-42.
13. Lee Sang H, et al. Inhibition of benzo(a)pyrene-induced mouse forestomach neoplasia by astaxanthin containing egg yolks. *Agric Chem Biotechnol* 1997;40(6):490-4.
14. Wang X, et al. Astaxanthin-rich algal meal and vitamin C inhibit *Helicobacter pylori* infection on BALB/cA mice. *Antimicrob Agents Chemother* 2000 Sep;44(9):2452-7.
15. Snodderly DM. Evidence for protection against age-related macular degeneration by carotenoids and antioxidant vitamins. *Am J Clin Nutr* 1995;62(suppl):1448S-61S.
16. Gerster H. Antioxidant protection of the ageing macula. *Age Ageing* 1991;20:60-9.
17. Tso MO, Lam T-T. Method of retarding and ameliorating central nervous system and eye damage. US Patent 5,527,533 (1996).
18. Landrum JT, et al. Analysis of zeaxanthin distribution within individual human retinas. *Meth Enzymol* 1999;299:457-67.
19. Murillo E. Hypercholesterolemic effect of canthaxanthin and astaxanthin in rats. *Arch Latinoam Nutr* 1992 Dec;42(4):409-13.
20. Ono A, et al. A 13-week subchronic oral toxicity study of haematococcus color in F344 rats. *Kokuritsu Iyakuhiin Shokuhin Eisei Kenkyusho Hokoku* 1999;(117):91-8.
21. Shimidzu, N, et al. Carotenoids as singlet oxygen quenchers in marine organisms. *Fisheries Science* 1996;62(1): 134-7

AQUACULTURE VALUES ASTAXANTHIN

1. Johnson EA, An G-H. Astaxanthin from microbial sources. *Critical Rev Biotechnol* 1991;11:297.
2. Bowen, et al. Aquasearch technical report TR.2102.001. Aquaxan HD algal meal use in aquaculture diets: enhancing nutritional performance and pigmentation. 1999.

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