Supplement Monographs
The major deficiency syndrome of vitamin C is scurvy. Symptoms of scurvy include inflamed and bleeding gums, petechiae, ecchymoses, follicular hyperkeratosis, coiled hairs, perifollicular hemorrhages, impaired wound healing, dry eyes and mouth (Sjögren’s syndrome), arthralgia, joint effusions, muscle weakness, myalgia, fatigue, depression, frequent infections, anemia, anorexia, diarrhea, and pulmonary and kidney problems that can lead to coma and death. All systems of the body are affected by scurvy.

The antiscorbutic factor was isolated from the ox adrenal cortex in 1927 by the Hungarian biochemist and Nobel laureate Albert Szent-Györgyi and his colleagues, although at the time Szent-Györgyi didn’t know that it was the antiscorbutic factor. In fact, his interest then was not in vitamins at all but in biological oxidation and reduction, and he was looking for reducing substances in extracts of the adrenal cortex. What was later to be known as ascorbic acid, Szent-Györgyi called “C XII” since it was the 12th substance prepared and examined in his work on tissue oxidation and the function of the adrenal cortex. He later discovered that C XII was indeed vitamin C, the antiscorbutic factor, that its empirical formula was C₆H₈O₆ and that the molecule was a carbohydrate, most likely a sugar derivative. He submitted a paper on his discovery, which he named Ignose (from “ignosco”—“I don’t know” in Latin—and “-ose” to indicate that it was a member of the sugar family). However, the editor of the journal rejected that name and also the next one that Szent-Györgyi came up with, “Godnose.” The editor suggested “hexuronic acid” to indicate that it had six carbons and was a sugar acid similar to glucuronic acid. Szent-Györgyi gave in and accepted that name, which shortly was to change to ascorbic acid. Szent-Györgyi actually didn’t know the exact structure of ascorbic acid, which explains Ignose and Godnose. It was the chemist and also Nobel laureate Walter Haworth who actually deciphered the structure. Szent-Györgyi found a rich source of ascorbic acid in the fruit of the Hungarian red pepper or paprika (Capsicum annuum). He also found some other interesting reducing agents in paprika. He called these substances vitamin P. They were the first flavonoids identified. In 1932, the American biochemist Glen King and his colleagues isolated ascorbic acid from lemon juice, which is where the vitamin C story first began. Well, actually lime juice, but close enough.

Many of the symptoms of scurvy, particularly those having to do with connective tissue, can be explained by the known biochemical roles of vitamin C, particularly its role as a cofactor for prolyl and lysyl hydroxylase, enzymes important in the formation of collagen. Collagen synthesized in the absence of ascorbic acid—as occurs in scurvy—cannot properly form fibers, resulting in blood-vessel fragility, among other defects. In the prolyl and lysyl hydroxylase reactions, as well as in most of the biochemical reactions ascorbic acid participates in, it acts as a reducing agent. In these reactions, the vitamin reduces ferric and cupric ions to their ferrous and cuprous states, forms which are required for the reactions to proceed.
Ascorbic acid is also involved in the biosynthesis of other connective-tissue components, including elastin, fibronectin, proteoglycans, bone matrix and elastin-associated fibrillin. It also appears to play a role in collagen gene expression and cellular procollagen secretion.

The fatigue and weakness of scurvy may be due to L-carnitine deficiency. Ascorbic acid is a cofactor for crucial reactions in the carnitine biosynthetic pathway.

Ascorbic acid is involved in modulating iron absorption, transport and storage. It aids in the intestinal absorption of iron by reducing ferric iron to ferrous iron and may stimulate ferritin synthesis to promote iron storage in cells. It is involved in the biosynthesis of corticosteroids and aldosterone, the conversion of cholesterol to bile acids and it functions as a reducing agent for mixed-function oxidases.

For all of this, ascorbic acid is best known for its antioxidant properties and its possible role in the prevention of certain chronic degenerative disorders, such as coronary heart disease and cancer. In fact, ascorbic acid may be the most important water-soluble antioxidant in the body.

The daily dietary intake of vitamin C necessary to prevent scurvy is about 5 to 10 milligrams. Scurvy is rare in developed countries, since most people living in these countries typically consume much more than this amount.

About 90% of vitamin C in the average diet comes from fruits and vegetables. Peppers—sweet green and red peppers and hot red and green chili peppers—are especially rich in vitamin C. Other good sources include citrus fruits and juices, brussels sprouts, cauliflower, kale, collards, mustard greens, broccoli, spinach and strawberries. Nuts and grains contain very little vitamin C. Cooking destroys vitamin C activity.

About 5% to 10% of the total vitamin C content of fresh fruits and vegetables is comprised of dehydroascorbic acid. In the case of processed foods, dehydroascorbic acid makes up about 30% of the vitamin C content. D-ascorbic acid (erythorbic acid or isoascorbic acid), the epimer of L-ascorbic acid, is frequently added to food as an antioxidant preservative. Erythorbic acid has very low vitamin C activity.

In addition to being known as ascorbic acid and L-ascorbic acid, vitamin C is also known as 2, 3-didehydro-L-threo-hexano-1, 4-lactone, 3-oxo-L-gulofuranolactone, L-threo-hex-2-enonic acid gamma-lactone, L-3-keto-threo-hexuronic acid lactone, L-xyl-o-ascorbic acid and antiscorbutic vitamin. It is abbreviated AA. Ascorbic acid is a crystalline, watersoluble substance with a pleasant (to some), sharp acidic taste. Its molecular weight is 176.13 daltons, and its molecular formula is C₆H₇O₆. The structural formula of vitamin C is represented as follows:

![Vitamin C](image)

The other form of vitamin C is the oxidation product of L-ascorbic acid, L-dehydroascorbic acid or DHA.

**Vitamin C with Bioflavonoids**

Vitamin C with bioflavonoids is a mixture of vitamin C, either as ascorbic acid or as an ascorbate, with flavonoids. Typically, the flavonoids are citrus flavonoids and are derived from lemons, oranges and grapefruits. It is believed that flavonoids work synergistically with vitamin C. This belief originates from the work and writings of the Hungarian biochemist Albert Szent-Gyögyi, the co-discoverer of ascorbic acid. Szent-Gyögyi also isolated substances from citrus fruits and Hungarian paprika which he called vitamin P. Vitamin P is now referred to as bioflavonoids or flavonoids. Flavonoids are not vitamins.

Szent-Gyögyi believed that bioflavonoids and vitamin C worked synergistically to maintain blood capillary health and prevent capillary fragility. There is some *in vitro* evidence that flavonoids and vitamin C do work synergistically. One study showed that ascorbic acid acts synergistically with the flavonoid quercetin to protect cutaneous tissue cells in culture against oxidative damage induced by glutathione deficiency. However, there is, as yet, no good evidence that vitamin C and flavonoids work synergistically *in vivo*. A recent study, in cell culture, suggested that flavonoids may even inhibit the uptake of vitamin C into cells.

Flavonoids have biological effects independent of any interaction with vitamin C. (See various monographs on flavonoids.) Flavonoids from grapefruit include quercetin, naringenin and kaempferol. Lemon flavonoids include hesperidin (hesperitin 7-O-beta-rutinoside) and eriocitrin (eriodictyol 7-O-beta-rutinoside). These flavonoids, along with rutin and others, may be found in vitamin C/bioflavonoid supplements. Some formulations use flavonoids from the sour orange *Citrus aurantium*.

**Effervescent Vitamin C**

Effervescent vitamin C is comprised of L-ascorbic acid, citric acid and sodium bicarbonate. It is similar to Alka Seltzer with ascorbic acid added. When the tablet is placed in water, the citric acid reacts with sodium bicarbonate to form...
sodium citrate and carbon dioxide. Also, some sodium bicarbonate reacts with ascorbic acid to form some sodium ascorbate. Some find effervescent C a more tolerable supplement than ascorbic acid.

ACEROLA VITAMIN C
Acerola vitamin C is vitamin C derived fromacerola fruit. Acerola is the fruit of the small tree or shrub known as Malphighia glabra L. Malphighia glabra is native to the Antilles and northern South America. Acerola is also known as Barbados cherry, Antilles cherry, West Indies cherry, Puerto Rican cherry, cerezo, cereja-das-antilhas and cereja-do-pará. In 1945, the Barbados cherry was analyzed by researchers at the School of Medicine, University of Puerto Rico, and was found to be very rich in vitamin C. Interestingly, the analysis was inspired by the use of the fruit for colds by the local people.

Acerola is one of the richest sources of vitamin C in the world. The vitamin C content of the fruit depends on ripeness, seasons, climates and localities. Content is highest when the fruit is still green and lowest when ripe. The vitamin C content of unripe fruits can range up to 4.7 grams per 100 grams of fruit or 4.7% and is about 2 grams per 100 grams or 2% in very ripe fruit. For comparison, the vitamin C content of a peeled orange is 0.05% or 50 milligrams per 100 grams. Acerola also contains flavonoids, other vitamins, such as thiamin, riboflavin, niacin, pantothenic acid and beta carotene, and minerals, such as magnesium and potassium.

Malphighia glabra has also shown active anti-fungal properties. Folk medicine uses of acerola include treatment of liver ailments, diarrhea, dysentery, coughs, colds and sore throats.

ROSE HIP VITAMIN C
Rose hips are the fruit of roses. The rose hip is the swollen ovary of the flower which produces seed after the petals of a blossom wither and fall. Once the petals have fallen off a rose all that remains attached to the stem is the rose hip. Rose hips are rich sources of Vitamin C. In fact, one species, Rosa rugosa Thunb, contains the highest amount of vitamin C of any organism in the world. Rosa rugosa Thunb rose hips can contain up to 7 grams of vitamin C per 100 grams of rose hips or 7%. Acerola, the next richest source of natural vitamin C produces up to 4.7% vitamin C, and, for comparison, the peeled orange contains 0.05% vitamin C.

During World War II, England, Norway and Sweden were faced with a scurvy crisis. Since the war had restricted normal shipping, the British could not obtain enough citrus fruit for vitamin C. Children began showing the symptoms of early scurvy. The British discovered rose hips to be an excellent source of vitamin C and made the fruit of the rose into teas, soups and syrups. The children received these supplements daily, and this prevented any problem with scurvy.

Rose hips are the major source of natural vitamin C. A few species are used to obtain the vitamin, including Rosa canina, Rosa mosqueta and Rosa rugosa Thunb. In addition to vitamin C, rose hips contain such carotenoids as beta-carotene, lycopene, zeaxanthin, rubixanthin, gazzanixanthin, beta cryptoxanthin, gamma-carotene, lutein, violaxanthin, and antheraxanthin. They also contain flavonoids, catechins, polyphenols, procyanidins and pectins.

Rose hips have other applications. The oil extracted from its seeds is included in many cosmetic preparations for its high content of alpha-linolenic acid (45%-50%) and linoleic acid (40%). The fruit has been used as food, mainly for preparing jams, teas and alcoholic beverages.

REDUCED-ACIDITY VITAMIN C
Reduced-acidity vitamin C consists of a mixture of 50% ascorbic acid and 50% sodium ascorbate. Some find this form of vitamin C a more tolerable supplement than ascorbic acid. Since the first pKa of ascorbic acid is 4.2, the pH of the mixture dissolved in water would be 4.2. Reduced-acidity vitamin C is also known as buffered vitamin C.

NON-ACID VITAMIN C
Non-acid vitamin C consists of an ascorbate salt of sodium or calcium which has a neutral pH when dissolved in water. The calcium salt consists of two molecules of ascorbate and one atom of calcium. The molecular formula is C12H14CaO12. Calcium ascorbate is freely soluble in water. The sodium salt consists of one molecule of ascorbate and one atom of sodium. The molecular formula is C6H7NaO6. Some find sodium ascorbate and calcium ascorbate more acceptable forms for vitamin C supplementation.

ASCORBATE AND VITAMIN C METABOLITES
Ascorbate and vitamin C metabolites refer to marketed vitamin C supplements containing vitamin C in a salt form, typically as calcium ascorbate, and vitamin C metabolites. Vitamin C metabolites can include the aldonic acids L-threonic acid, L-xylonic acid and L-lyxonic acid. Typically, the vitamin C metabolite present in these products is L-threonic acid, also known as 2, 3, 4-trihydroxy-[three]butanoic acid. L-threonic acid is usually also present as the calcium salt or calcium L-threonate, and the percentage of calcium L-threonate in the product is usually 1% of the amount of ascorbate. That is, a tablet supplying 500 milligrams of ascorbate would supply 5 milligrams of L-threonate.

Ascorbate and vitamin C metabolites are sometimes referred to as metabolite-supplemented ascorbate. Some in vitro studies have shown that the addition of L-threonate to
ascorbate enhances the transfer efficiency of ascorbate into cells. Animal studies have reported increased absorption and higher retention of vitamin C when the animals were supplemented with ascorbate plus threonate than when supplemented with ascorbate alone. One cell-culture study showed that the addition of threonate to ascorbate enhanced the production of collagenous protein and mineralized tissue when compared with ascorbate alone. The authors concluded that this finding could have relevance with respect to wound healing and bone regeneration.

Although the in vitro and animal studies appear interesting, what is wanting are well-designed and well-executed clinical trials in humans to determine if vitamin C metabolites, such as L-threonate, positively affect vitamin C status.

**ACTIONS AND PHARMACOLOGY**

**ACTIONS**

Vitamin C has antioxidant activity. It may also have antiatherogenic, anticarcinogenic, antihypertensive, antiviral, antihistaminic, immunomodulatory, ophthalmoprotective and airway-protective actions. Vitamin C may aid in the detoxification of some heavy metals, such as lead and other toxic chemicals.

**MECHANISM OF ACTION**

Vitamin C is arguably the most important water-soluble biological antioxidant. It can scavenge both reactive oxygen species and reactive nitrogen species. Ascorbic acid or, more specifically, L-ascorbate is an excellent reducing agent, and it acts as a cofactor in various biochemical reactions to reduce the transition metals, iron and copper.

Ascorbate can be oxidized by most reactive oxygen and nitrogen species thought to play roles in tissue injury associated with various diseases. These species include superoxide, hydroxyl, peroxy and nitro oxide radicals, as well as such non-radical reactive species as singlet oxygen, peroxynitrite and hypochlorite. By virtue of this scavenging activity, ascorbate inhibits lipid peroxidation, oxidative DNA damage and oxidative protein damage.

Ascorbate is oxidized by reactive oxygen and nitrogen species to the semidehydroascorbate radical that is either reconverted to ascorbate via the enzyme NADH semidehydroascorbate reductase or is converted to dehydroascorbate. Dehydroascorbate in turn can be converted back to ascorbate via glutathione-dependent enzymes or catabolized.

Ascorbate can act as a secondary antioxidant. At least in vitro, ascorbate regenerates the major lipid antioxidant alpha-tocopherol from the alpha-tocopheroyl radical form. Ascorbate may also participate in regenerating and sparing alpha-tocopherol in vivo, though this has not been clearly demonstrated. Vitamin C does preserve intracellular reduced glutathione concentrations.

The possible anti-atherogenic activity of vitamin C may be explained in a few ways. Oxidation of low-density lipoprotein (LDL) is thought to be a key early step in atherogenesis. Vitamin C protects against LDL peroxidation by scavenging peroxyl radicals in the aqueous phase. Vitamin C may enhance endothelial function by promoting the synthesis of nitric oxide (also known as NO and EDRF for endothelium-derived relaxing factor) or by preventing its inactivation by scavenging superoxide radicals. Superoxide reacts with nitric oxide to form peroxynitrite. High concentrations of vitamin C are required to prevent the interaction of superoxide with nitric oxide, extracellularly. Although such high plasma concentrations are feasible if vitamin C is given parenterally, they are likely not to occur with oral administration of vitamin C.

As noted above, vitamin C helps preserve intracellular reduced glutathione concentrations. This activity likely helps maintain nitric oxide levels and potentiates its vasodilatory effects. Oral vitamin C can reach high enough concentrations intracellularly to scavenge superoxide radicals. Thus, intracellular sources of superoxide that impair nitric oxide may be scavenged by oral vitamin C. Recently, it has been found that ascorbic acid enhances nitric oxide synthase activity by increasing intracellular tetrahydrobiopterin.

Vitamin C may modulate prostaglandin synthesis to favor the production of eicosanoids with antithrombotic and vasodilatory activity. The possible sparing and regeneration of alpha-tocopherol by vitamin C could be yet another factor in the vitamin’s possible anti-atherogenic action.

Vitamin C’s possible anticarcinogenic effects may be accounted for, in part, by its ability to detoxify carcinogens, as well as its ability to block carcinogenic processes through its antioxidant activity. Vitamin C can prevent the formation of such carcinogens as nitrosamines in foods and in the gastrointestinal tract and can detoxify such chemical mutagens and carcinogens as anthracene, benz[a]pyrene, organochlorine pesticides and heavy metals. High concentrations of ascorbic acid in gastric juice may reduce the risk of gastric cancer by inhibiting, as noted, the formation of carcinogenic N-nitroso compounds. Additionally, increased oxidative stress to the gastric mucosa has been reported in *Helicobacter pylori*-associated gastritis, a condition that predisposes to gastric cancer. There is preliminary evidence that vitamin C can inhibit growth of *Helicobacter pylori*.

Evidence appears to suggest that vitamin C may have cancer-preventive activity, at least for certain types of cancer. However, the role of vitamin C, if any, in the treatment of cancer remains very unclear. A cell-culture study of human
The possible immunomodulatory activity of vitamin C may also be due, in part, to an antihistaminic effect of the vitamin. Vitamin C may enhance neutrophilic chemotaxis indirectly by reducing immunosuppressive effects of histamine. Some studies have shown that vitamin C, in vitro, enhances mitogen-stimulated lymphocyte proliferation, delayed-type hypersensitivity (DTH) response to skin antigens, natural killer cell activity and neutrophil chemotaxis. However, other studies have shown no effect of the vitamin on these and other indices of immune function.

Some studies suggest a protective effect of vitamin C supplementation against cataracts. Age-related lens opacities are thought to be due to oxidative stress. Ocular tissue concentrates vitamin C, and the antioxidant action of the vitamin could account for its possible effect in protection against cataracts.

Vitamin C may protect against asthma and other obstructive pulmonary diseases, as well as protect the airways against the effects of allergens, viral infections and irritants in some. Allergens, viruses and irritants, including ozone, nitrogen oxides and sulfur oxides, subject the airways to increased oxidative stress which can lead to bronchoconstriction. The possible protective action of vitamin C appears clearly due to its antioxidant properties.

The antioxidant properties of vitamin C can also account for its role in protecting against the tissue-damaging effect of some toxic chemicals and heavy metals. High serum levels of ascorbic acid have been reported to be associated with a decreased prevalence of elevated blood lead levels. The mechanism of the possible lead-lowering action of vitamin C is unclear. One study compared the chelating properties of ascorbic acid and the known lead-chelating agent EDTA and found them to have equivalent activity with respect to lead.

**PHARMACOKINETICS**

Absorption of vitamin C from the lumen of the small intestine depends on the amount of dietary intake. At a dietary intake of 30 milligrams daily, the vitamin is nearly completely absorbed from the lumen of the small intestine into the enterocytes. At an intake of 30 to 180 milligrams daily, about 70% to 90% is absorbed. About 50% of a single dose of 1 to 1.5 grams is absorbed. The percentage of a single dose absorbed decreases with increasing amounts. For example, only 16% of a single dose of 12 grams is absorbed. Maximum vitamin C absorption of large doses is attained by ingestion of several spaced doses throughout the day rather than by a single large dose. Further, sustained-release forms of large doses will give a higher efficiency of absorption than an equivalent dose that is not sustain-released. The type of food consumed does not appear to affect the absorption of supplemental vitamin C or vitamin C found in food.

The intestinal absorption of vitamin C from foods and from supplements, up to about 500 milligrams, occurs via a sodium-dependent active transport process. At doses higher than 500 milligrams, diffusion processes come into play. The major intestinal vitamin C transporter is SVCT1 (sodium-dependent vitamin C transporter 1). Some ascorbic acid may
be oxidized to dehydroascorbic acid and transported into enterocytes via glucose transporters. Dietary dehydroascorbic acid is absorbed from the lumen of the small intestine into the enterocytes in such a manner. All dehydroascorbic acid within the enterocytes is reduced to ascorbic acid via reduced glutathione, and ascorbic acid leaves the enterocytes to enter, first, the portal and, subsequently, the systemic circulation. Ascorbic acid is distributed to the various tissues of the body.

Higher levels of ascorbic acid are found in the pituitary gland, the adrenal glands, the various white blood cells and the brain. Ascorbic acid itself cannot cross the blood-brain barrier. In order to enter the brain, ascorbic acid is first oxidized to dehydroascorbic acid or DHA. DHA is then transported across the blood-brain barrier by facilitative diffusion via glucose transporter 1 (GLUT1). DHA is next transported through GLUT1 at the surface of the blood-brain barrier endothelial cells. DHA is transported out of the endothelial cells through GLUT1. DHA in the brain is reduced to ascorbic acid. Ascorbic acid, once formed, is essentially trapped in the brain since it cannot be transported through GLUT1.

Ascorbic acid appears to be transported into intestinal cells, liver cells and kidney cells by a sodium-dependent active transport process via SVCT1 (sodium-dependent vitamin C transporter 1). The transporter SVCT2 (sodium-dependent vitamin C transporter 2) appears to aid in the transport of vitamin C into the aqueous humor of the eyes. Uptake of ascorbic acid into neutrophils appears to be by facilitative diffusion via GLUT1.

Regarding the metabolism of ascorbic acid, it is oxidized to dehydroascorbic acid which can either be reduced back to ascorbic acid or hydrolyzed to diketogulonate. Other metabolites include oxalic acid, threonic acid, L-xylose and ascorbate-2-sulfate. The principal route of excretion of ascorbic acid and its metabolites is via the kidney. In order to maintain ascorbic acid homeostasis, very little unmetabolized ascorbate is excreted with dietary intakes up to about 80 milligrams daily. Renal excretion of ascorbate increases proportionately with higher doses. As mentioned earlier, as the dose of supplemental ascorbic acid increases, the percentage of its absorption proportionately decreases. Consequently, there is significant fecal excretion of ascorbic acid with high supplemental intakes of the vitamin.

**INDICATIONS AND USAGE**

Vitamin C may be helpful in chronic diseases characterized by oxidative damage to biological molecules. Though vitamin C also has a pro-oxidant potential under some circumstances, fears raised in that regard in recent years appear overblown. There is currently no credible evidence for oral vitamin C pro-oxidant damage in humans except, possibly, in rare circumstances involving iron overload.

Vitamin C’s antioxidant activity, on the other hand, is well established, and that activity may be helpful in the prevention of some cancers and cardiovascular disease. Vitamin C may also be helpful in protecting against some of the lipid oxidation caused by smoking. Vitamin C’s demonstrated ability to reduce some forms of oxidative DNA damage and indications that it may also reduce protein oxidation under some circumstances further suggest that it may be of benefit in smokers and some with chronic stress and disease, in general. Considerable excitement has attended recent in vitro and in vivo animal research findings that injected vitamin C may have potent anticancer effects in a number of established malignancies, renewing interest in vitamin C not only as a possible cancer preventive but also as a potentially potent cancer interventive. These same findings have suggested that Vitamin C may also have some anti-infective potential greater than previously acknowledged.

Vitamin C may also be useful as an immune stimulator and modulator in some circumstances. Claims that it is a “cure” for common colds are unsubstantiated, although several studies have shown that vitamin C can significantly reduce the duration and severity of colds in some and reduce incidence in others. There is also preliminary evidence that vitamin C can be useful in ameliorating some other respiratory infections.

Vitamin C may help prevent cataracts.

Recently it was demonstrated that vitamin C can inhibit growth of *Helicobacter pylori* and may thus be protective against some ulcers and gastric carcinomas. There is also the suggestion in a recent report that low serum levels of ascorbic acid may be associated with a higher incidence of gall bladder disease in women. In another recent report, vitamin C supplementation was associated with reduced risk of reflex sympathetic dystrophy after wrist fracture. It may be of benefit in some burn victims and may be helpful, generally, in promoting wound healing and gum health.

Vitamin C has previously shown some benefit in some individuals with asthma, although a recent review concluded that the vitamin C asthma data remain inconclusive. Whether it might also be useful in some other airway disorders/impairment, such as those present in cystic fibrosis, remains unclear and largely untested. There is a preliminary indication that it might be helpful in Charcot-Marie-Tooth disease, the most common hereditary peripheral neuropathy. There is no convincing evidence that it is useful in Alzheimer’s disease. A strong inverse association between plasma vitamin C levels and type 2 diabetes mellitus risk has been
noted recently. Effects on muscle and endurance performance are unclear.

RESEARCH SUMMARY
Vitamin C's antioxidant effects are well established. It has been reported to protect plasma lipids from oxidative damage. It also significantly protects DNA and protein from various oxidative processes, as demonstrated in numerous studies.

There is still controversy around claims that vitamin C can be a dangerous pro-oxidant in humans. These claims are now generally discounted, and the research that led to these fears has been widely challenged as being flawed in a number of respects. One researcher recently reviewed this controversy and concluded: "there is nothing in current data to worry members of the public who take ascorbate supplements."

Other researchers have also recently reviewed this controversy, noting that in vitro observations of DNA damage arising in the presence of vitamin C and redox-active transition metal ions are unlikely to have relevance in vivo. The damaging effect demonstrated in vitro, these researchers point out, "requires the availability of free, redox-active metal ions and a low ratio of vitamin C to metal ion, conditions unlikely to occur in vivo under normal circumstances. Furthermore, it was shown recently that in biological fluids such as plasma, vitamin C acts as an antioxidant toward lipids even in the presence of free, redox-active iron . . . there is no convincing evidence for a pro-oxidant effect of vitamin C in humans." However, although this is the case for orally administered vitamin C, the vitamin may indeed have a pro-oxidant effect when administered parenterally (see below).

On the other hand, vitamin C's antioxidant activity is marked and appears to play an important role in its possible cardioprotective activity. Several studies have shown that vitamin C, either alone, or in combination with other nutrients significantly inhibits LDL-cholesterol oxidation. This effect is most consistent when vitamin C is combined with vitamin E and/or beta-carotene, but it has also been observed when vitamin C is used alone. In the latter case, some hypothesize that it works by sparing or recycling vitamin E, an activity that has been observed in vitro. Results have been mixed in smokers in whom lipid oxidation is a serious problem. One of the better designed studies, utilizing a particularly sensitive measure of lipid oxidation, found that heavy smokers benefited from 2,000 milligrams of vitamin C administered for only five days, as measured by a significant reduction in a specific lipid oxidation marker, the F2 isoprostane 8-epi-PGF2-alpha.

Where there have been discrepancies in results from lipid (and other) biomarkers studies, some researchers attribute these, in part, to the failure of some investigators to differentiate between subjects whose tissues are already saturated with vitamin C at baseline and those whose tissues are not thus saturated. Even dietary, non-supplemental, vitamin C intake, they argue, can readily result in saturation sufficient to rule out further reductions in oxidative damage, no matter what supplemental dose is administered.

Vitamin C supplementation has also been reported, in some studies, to significantly reduce total serum cholesterol. Some others have not shown this benefit. And there have been several observational reports associating high plasma vitamin C concentrations with higher levels of HDL-cholesterol.

Platelet aggregation has been reduced in two studies utilizing 2,000-3,000 milligrams of vitamin C daily for one to six weeks. No effect was noted on platelets in another study using 250 milligrams of vitamin C daily for eight weeks. Leukocyte adhesion to endothelium, an activity implicated in atherogenesis, was significantly inhibited in smokers receiving 2,000 milligrams of vitamin C daily for 10 days.

Several studies have shown that vitamin C has positive effects on hypertension. Here, too, there have been some conflicting results, but the preponderance of evidence suggests a positive effect. Epidemiological studies also consistently show that lower vitamin C intake is associated with hypertension. In one recent randomized, double-blind, placebo-controlled study, hypertensive patients received placebo or 500 milligrams of vitamin C daily for 30 days. Vitamin C resulted in a 13 mmHg reduction in systolic blood pressure. Placebo had no effects.

Several other studies have shown that both oral administration (1,000-2,000 milligrams) and intra-arterial infusion with vitamin C can exert significant, positive effects on vasodilation in coronary artery disease patients. Similar benefits have been found in several other test groups, including smokers and those with both type 1 and type 2 diabetes.

Vitamin C's potential impact on incidence of heart attack, stroke and death related to cardiovascular disease may be quite significant according to the findings of several epidemiological studies. In an analysis of findings from the First National Health and Nutrition Examination Survey, researchers found that "the relation of the standardized mortality ratio (SMR) for all causes of death to increasing vitamin C intake is strongly inverse for males and weakly inverse for females." Among males with the highest vitamin C intake, SMRs were 0.65 for all causes, 0.78 for all cancers and 0.58 for all cardiovascular disease. Among females with the highest vitamin C intake, SMRs were 0.90 for all causes, 0.86 for all cancers and 0.75 for all cardiovascular disease. Comparisons were made relative to the U.S. white population, for which the SMR was defined as 1.00.
In a 20-year follow-up study of a cohort of randomly selected elderly people in Britain, Scotland and Wales, mortality from stroke was highest in those with the lowest vitamin C status, as measured by dietary intake and plasma ascorbic acid concentration. Adjustments were made for age, sex and established cardiovascular risk factors. The association noted was independent of social class and other dietary variables. No association was found in this study between vitamin C status and risk of death from coronary artery disease, but the researchers noted this may have been due to the age of their observed population. "Factors that may predict premature death from coronary heart disease may become less important when measured in a population of elderly survivors," they noted. The subjects in this cohort were 65-74 years of age.

Recently, a five-year prospective population study of 1,605 Finnish men aged 42-60, who were free of atherosclerotic heart disease at baseline, concluded with these results: risk of myocardial infarction was considerably higher among those with the lowest baseline plasma vitamin C concentrations than among those with higher levels; 13.2% of those with the lowest levels suffered MIs versus 3.8% of those with higher levels.

What made this study particularly significant was its finding that increased risk of MI, in relation to plasma vitamin C concentrations, was confined to that group of subjects who were frankly deficient in vitamin C. In men with normal to high concentrations, there was no increased risk. This may have significance for some other studies that found no benefit from vitamin C in reducing cardiovascular disease risk.

It has been established by prior research that the Finnish population suffers high mortality from coronary heart disease and that many Finnish men have low plasma ascorbate concentrations. A reviewer of the Finnish study thus concluded that the finding in this study "that only individuals who are vitamin C-deficient are at increased risk may explain to some extent why no significant relationship was observed in many studies of relatively well-nourished populations."

This observation might apply, some believe, to the Nurses' Health Study and the Health Professionals' Study, both follow-up investigations that showed a relationship between increased vitamin E intake and reduced coronary heart disease risk but no similar relationship with respect to vitamin C.

As the reviewer further observed: "Both of these studies involved generally health-conscious study subjects. The vast majority of antioxidant-disease studies, even controlled intervention studies, involve generally healthy, well-nourished populations, primarily because these populations are much easier to study. The Finnish study results, therefore, provide a special perspective that may help us to understand the mixed results from past studies and better plan future studies."

Vitamin C has, experimentally, demonstrated an ability to protect against various cancers, most likely through its ability to inhibit DNA oxidation, through reactive nitrogen species scavenging and other antioxidant actions, as well as through its possible effects on the immune system, among other activities. There are numerous epidemiological and case-control studies showing a consistent relationship between higher dietary intakes of vitamin C and lower incidence of cancer, particularly colorectal, stomach, lung, breast, esophageal, oral cavity and larynx-pharynx cancers. In one review of 75 epidemiologic studies, 54 found significant evidence of reduced cancer risk in those with higher dietary vitamin C intake.

Several in vitro and animal studies have demonstrated benefits. Results of some animal studies suggested that vitamin C therapy could reduce the toxicity and/or increase the effectiveness of some standard cancer therapies. Currently some researchers have expressed fear that vitamin C might reduce the effectiveness of some radiation and cancer chemotherapies by reducing their toxicity in cancer cells, as well as in normal cells. This idea has neither been confirmed nor refuted in animal or human studies and requires further investigation. Meanwhile, other researchers have expressed doubts about this hypothesis. They point out, as noted above, that several experimental studies indicate that high doses of vitamin C not only protect normal cells from toxic cancer therapies but may simultaneously fight the cancer cells, as well.

Many population studies have found evidence of a vitamin C protective effect against some cancers. Some other studies, however, have been negative. One group of researchers reported a significant 29% reduction in risk of all cancer in males consuming 113 milligrams or more of vitamin C daily, compared with males consuming less than 82 milligrams daily. Another found that consumption of 300 milligrams of vitamin C daily, derived from diet and from supplementation, was associated with a 21% reduction in risk from all cancers in men compared with daily consumption of less than 49 milligrams daily.

In a review of many of the epidemiological studies, the authors noted: "Interestingly, virtually all of the studies in which vitamin C intakes were greater than 87 milligrams a day in the lowest intake group (quantile) found no or nonsignificant effects on cancer risk reduction with higher
intakes of vitamin C . . . . More studies investigating cancer risk in persons with lower vitamin C intakes are warranted."

Studies of those using higher dose vitamin C supplements have generally not shown protective effects against cancer, "possibly," these reviewers observed, "because the dietary intake of vitamin C was already sufficient for tissue saturation." Intervention trials with high dose vitamin C have also been mostly negative.

At present, there is evidence that vitamin C helps protect against a number of cancers. Generally amounts sufficient to exert preventive activity can be obtained from a diet that includes several servings of fruits and vegetables daily and/or through low-dose vitamin C supplementation.

Recently evidence has emerged that vitamin C may also have a potent interventive potential in cancer—but not via diet/supplementation but, rather, via injection. A few years ago, several researchers from various branches of the National Institutes of Health conducted an in vitro study, the results of which surprised many in the research world. These researchers exposed human Burkitt’s lymphoma cells to concentrations of ascorbic acid equal to what they determined could be achieved through injection (but not through oral administration). They cited pharmacokinetics studies that had demonstrated that 10 grams of ascorbic acid given intravenously can produce at least a 25-fold higher plasma concentration than can the same dose given orally. Their results demonstrated that the much higher levels achievable through the intravenous route effectively killed cancer but not normal cells, acting as a pro-drug to deliver extracellular hydrogen peroxide as the selective killing agent. Why the hydrogen peroxide generated by the ascorbate does not affect normal cells remains unknown. The cancer cell death occurred by apoptosis and pyknosis/necrosis. The researchers hypothesized that the hydrogen peroxide might target cancer cellular membrane lipids forming hydroperoxides or reactive intermediates that are quenched/repaired in normal cells but not in cancer cells. In any case, the researchers concluded that these findings have “major therapeutic implications” and not only for cancer but also possibly for numerous infections that have been shown to be susceptible to hydrogen peroxide attack. (Among these: some viruses, including hepatitis C.) They pointed as well to a possible therapeutic application of vitamin C in patients with chronic granulomatous disease—again via injection, not oral administration.

Very recently, some of these same researchers generated headlines around the world when they extended their in vitro observations to in vivo animal cancer models, again with notable positive results. In these experiments, the researchers delivered pharmacologic parenteral doses of ascorbate to mice bearing aggressive tumor xenografts. Single doses of the ascorbate produced significant, sustained ascorbate radical and hydrogen peroxide formation selectively within interstitial fluids of tumors but not in blood. Daily administration of ascorbate significantly reduced growth rates of established ovarian, pancreatic and glioblastoma tumors in the mice. The researchers showed as well that the same pharmacologic concentrations of ascorbate were easily achieved via vitamin C injection in humans. They concluded that ascorbate as a pro-drug may have benefits in cancers “with poor prognosis and limited therapeutic options.” Clearly further research is indicated and warranted.

Vitamin C has shown a variety of activities in the immune system. It has been shown, in animal and in vitro studies, to favorably modulate lymphocytes and phagocytes. It can regulate natural killer cells under some circumstances and affect production of cytokines, antibodies and complement components.

Because supplemental vitamin C was not shown, in several studies, to reduce the incidence of the common cold, many concluded that it was of no use whatever in colds. That is still the impression of some physicians, but it is probably an erroneous one. First, a few studies have, in fact, shown a reduction in incidence of colds. Most studies have been done in normally nourished subjects in western countries; these have, typically, shown no effect on incidence. But in three trials of subjects under acute physical stress, vitamin C supplementation resulted in a 50% reduction in common cold incidence. And in four British trials, there was an average 30% reduction in incidence among those receiving vitamin C. Dietary vitamin C intake is known to be low in the UK.

Placebo-controlled trials have consistently found that supplemental vitamin C, in doses of 1 gram or greater daily, alleviated the duration and severity of cold symptoms. In several of these studies, the alleviation has been significant. For unexplained reason, there seems to be a greater effect in children than in adults and possibly, a greater effect in males than in females. The best results have been obtained with 2-gram (or greater) daily doses. There was a 6% median reduction in cold duration in five studies in which adults were administered 1 gram of vitamin C daily. There was a median decrease of 26% in two studies of children given 2 grams of vitamin C daily. A recent review found no consistent evidence for vitamin C reducing the incidence of colds in the normal population, but it did find a strong positive effect among those exposed to brief periods of strenuous physical exercise and/or cold environments. An analysis of six trials involving a total of 642 skiers, marathon runners and soldiers on sub-arctic exercises indicated that vitamin C supplementation cut the risk of colds in half. The reviewers called for more therapeutic trials to further clarify
the vitamin’s potential in treating/preventing/shortening colds.

Vitamin C has also been found to be of benefit in patients with pneumonia and bronchitis. Incidence of pneumonia was significantly reduced in three controlled vitamin C studies, and substantial vitamin C treatment benefit was noted in elderly UK patients hospitalized with pneumonia or bronchitis.

There is evidence that supplemental vitamin C can inhibit the growth of *Helicobacter pylori* in both in vitro and animal studies. Thus it might have the potential to reduce the incidence of *H. pylori*-induced ulcers and subsequent gastric carcinoma. In vitro, high concentrations of vitamin C inhibited up to 90% of *H. pylori* growth. There was also significant inhibition of growth in animal experiments using oral administration of vitamin C.

High intake of vitamin C is strongly associated with reduced incidence of cataracts, according to the findings of case-control studies. In one study, intake of 300 milligrams or more per day was associated with a 70% reduction in risk. Another study found a 75% reduction in risk with daily intake of 490 milligrams or more per day, compared with intakes less than 125 milligrams per day. An intervention study using 120 milligrams of vitamin C daily produced a nonsignificant reduction in cataract risk of 22%, but a significant 36% reduction was observed in the same trial in subjects who consumed a multivitamin/mineral supplement. Laboratory work has shown that vitamin C can slow chemical reactions that lead to cataracts by causing various lens proteins to aggregate. This has been demonstrated in animal work and in the human eye.

In a study of women who took vitamin C for at least ten years, incidence of cataracts was significantly reduced compared with controls who did not take vitamin C. The vitamin C-supplemented women were only 23% as likely to develop cataracts compared with the women who did not take supplements. In women not taking supplements, mean daily intake of vitamin C was 130 milligrams per day, about twice the recommended intake but still less than one-third the average of women taking supplements.

Recently, serum ascorbic acid levels were found to be inversely related to prevalence of gall bladder disease among women but not among men. Previously, it was shown that vitamin C-deficient guinea pigs have a high incidence of gallstones. Further clinical investigation is warranted.

In another recent study, this one a double-blind, placebo-controlled trial of vitamin C in patients with conservatively treated wrist fractures, treatment with 500 milligrams of vitamin C daily for 50 days significantly reduced the incidence of reflex sympathetic dystrophy (RSD). Follow-up continued for one year. The researchers proposed that "this simple and cheap means of prevention could also be useful in the prophylaxis of RSD after other injuries, such as trauma of the foot or ankle, talar and calcaneal fractures, or crural fractures."

It was the use of vitamin C as an antioxidant therapy in dermal burns that led the researchers to believe that an antioxidant therapy might also be of benefit in preventing post-traumatic dystrophy (after wrist fracture). Researchers have found that vitamin C helps protect endothelial cells and reduces capillary permeability by reducing lipid peroxidation after burns. Some of these same mechanisms apparently account for reported beneficial effects of vitamin C in a variety of wounds, in addition to burns. There is some evidence that supplemental vitamin C may decrease permeability of gum surface tissue and may, by that and other mechanisms, help protect against periodontal gum disease.

Some studies have indicated that vitamin C can be of benefit in alleviating some of the symptoms of asthma. In one of these studies, a 500-milligram dose of vitamin C taken 90 minutes before exercise reduced bronchial spasms in some asthma sufferers. In another study, 1 gram of ascorbate daily reduced airway reactivity to various harmful inhalants in asthmatics. A recent review of the vitamin C asthma literature, however, found no convincing evidence (from randomized control trials) that the vitamin has an established role in the treatment of this disorder. The authors concluded that the data gathered to date are insufficient upon which to base any conclusion.

There is no evidence that vitamin C is helpful in Alzheimer’s disease. Vitamin C’s role in muscle metabolism and any possible benefit in endurance training remain to be delineated or demonstrated. In one recent study, oral administration of vitamin C was said to decrease muscle mitochondrial biogenesis and hamper training-induced adaptations in endurance performance in a small clinical trial. Oral doses of 1 gram daily were administered over an eight-week training period. Some of the findings of this study were derived from a concurrent animal study. Again, these data are insufficient for reaching any meaningful conclusion.

Recently, a strong inverse association was noted between plasma vitamin C levels and the risk of new-onset type 2 diabetes mellitus. Fruit and vegetable intake, to a lesser degree, was also inversely associated with this risk.

Finally, an intriguing study has suggested that ascorbic acid might be helpful in the treatment of Charcot-Marie-Tooth disease, the most common hereditary peripheral neuropathy, affecting 1 in 2,500 people. The only other treatments for this disease are physical rehabilitation and corrective sur-
gery. This is a disease characterized by abnormal myelination of the peripheral nerves with consequent progressive weakness and atrophy of the distal muscles of the limbs. In this mouse model of the disease, ascorbate, a known promoter of myelination, substantially ameliorated the condition, reducing the expression of what is believed to be the responsible gene to a level below that required to induce the disease phenotype. The researchers, noting the absence of good alternatives, concluded that vitamin C "offers an immediate therapeutic possibility for patients with the disease."

**CONTRAINDICATIONS, PRECAUTIONS, ADVERSE REACTIONS**

**CONTRAINDICATIONS**

Vitamin C is contraindicated in those with known hypersensitivity to the substance or to any ingredient in a vitamin C-containing product.

*Rose hip vitamin C*

Rose hip vitamin C is contraindicated in those with known hypersensitivity to rose hips. There are reports of allergic reactions in those working with rose hips.

**PRECAUTIONS**

Although oxalic acid is formed when ascorbic acid is metabolized, this is highly unlikely to cause renal problems in healthy individuals without preexisting renal problems or who are not predisposed to increased crystal aggregation. Those with preexisting kidney stone disease or a history of renal insufficiency, defined as serum creatine greater than 2 and/or creatinine clearance less than 30, should exercise caution in the use of higher than RDA amounts of vitamin C (see Dosage and Administration).

Ascorbic acid is involved in modulating iron absorption and transport. It is highly unlikely that healthy individuals who take supplemental vitamin C will have any problem with iron overload. On the other hand, those with hemochromatosis, thalassemia, sideroblastic anemia, sickle cell anemia and erythrocyte G6PD deficiency might have such a problem if they use large amounts of vitamin C.

Pregnant women and nursing mothers should avoid using supplemental doses of vitamin C higher than RDA amounts.

**ADVERSE REACTIONS**

In healthy adults, oral doses up to 3 grams daily of vitamin C are unlikely to cause adverse reactions. The most common adverse reaction in those who take oral doses greater than 3 grams daily are gastrointestinal and include nausea, abdominal cramps, diarrhea and flatulent distention. These reactions are attributed to the osmotic effect of unabsorbed vitamin C passing through the intestine. Some advocates of megadose vitamin C use recommend titrating the daily dose of vitamin C to what they refer to as "bowel tolerance", i.e., the point at which the user begins experiencing diarrhea. This is not recommended.

Rare adverse reactions have been reported in healthy individuals taking high oral doses of vitamin C. These include elevation of serum glucose in an adult male taking 4.5 grams daily, a gastrointestinal obstruction in a 66-year-old woman taking 4.5 grams daily of ascorbic acid and esophagitis in one person taking a single 500 milligram dose. Daily ingestion of high-dose vitamin C is generally regarded as largely innocuous. However, vitamin C-induced hyperoxaluria, although rare, has been reported. It was reported (July 2008) that a patient admitted to a hospital in New Zealand developed acute renal failure secondary to vitamin C-induced hyperoxaluria, from which the patient died.

**INTERACTIONS**

**DRUGS**

*Aluminum-containing antacids:* The intake of large doses of vitamin C used at the same time as aluminum-containing antacids has been reported to increase urinary aluminum excretion, suggesting increased aluminum absorption from these antacids. However, this is not well documented.

*Aspirin:* Chronic use of high dose aspirin may lead to impaired vitamin C status.

*Chemotherapeutic agents:* Vitamin C may potentiate the antineoplastic activity of cisplatin, doxorubicin and paclitaxel. It may also help ameliorate the cardiotoxic effect of doxorubicin and the nephrotoxic effect of cisplatin. This is based on *in vitro* and animal studies. There is a concern by some researchers that supplemental doses of vitamin C may diminish the efficacy of some chemotherapeutic agents. Ascorbic acid has been found to enhance arsenic trioxide-induced cytotoxicity in multiple myeloma cells. It has also been found to overcome drug resistance in myeloma and to significantly increase the anti-myeloma effects of both arsenic trioxide and melphalan in cell culture models and in animal models. Arsenic trioxide is an anticancer drug with multiple actions, and a number of clinical studies are examining the possible synergistic effect that vitamin C may have when administered along with arsenic trioxide. In all of these cases, vitamin C is given parenterally and not orally.

However, a recent report found that vitamin C may antagonize the cytotoxic effects of a number of antineoplastic drugs, including doxorubicin, vincristine, methotrexate, cisplatin and imatinib mesylate. This was based on a preliminary *in vitro* study and requires follow-up before any conclusions can be drawn.

*Estrogen:* Ascorbic acid may enhance 17 beta-estradiol inhibition of oxidized LDL formation.
Propranolol: Ascorbic acid may affect both the absorption process and the first pass metabolism of propranolol. Heart rate has been found to decrease less when propranolol was administered with ascorbic acid, when compared to controls. The interaction has little biological importance.

Vitamin C/Bioflavonoid combinations and drugs that inhibit cytochrome P-450 3A4: Preparations containing grapefruit flavonoids may interact with some drugs. Some drugs have up to a three-fold greater bioavailability when coadministered with grapefruit juice. It is thought that the grapefruit flavonoid naringenin plays some role in this effect. Naringenin and/or other substances found in grapefruit juice inhibit cytochrome P-450 3A4 (CYP 3A4). Drugs affected include the calcium channel blocker felodipine, as well as carbamazepine, cyclosporine, lovastatin, simvastatin, saquinavir and nisoldipine. Those taking these drugs need to exercise some caution in the use of any grapefruit products.

NUTRITIONAL SUPPLEMENTS

Copper: One study showed that high doses of vitamin C negatively affected copper status in men. Other studies have not shown such effects.

Flavonoids: Vitamin C may act synergistically with various flavonoids. This is the basis of combining flavonoids with vitamin C in some supplements. However, it is not known if any synergism occurs to any extent in humans. There is a report that the vitamin acts synergistically with the flavonoid quercetin to protect cutaneous cells against oxidative damage. The study was performed with cells in culture. There are other reports, again from cell culture studies, that certain flavonoids such as quercetin and hesperetin may inhibit the uptake of vitamin C into cells.

Glutathione: Ascorbic acid may help maintain reduced glutathione levels in cells.

Iron: Vitamin C used concomitantly with nonheme iron supplements may increase the uptake of iron. This may cause problems in those with high iron stores or with propensity for iron overload, such as those with hemochromatosis, sideroblastic anemia, sickle cell anemia, thalassemia and erythrocyte G6PD deficiency.

Selenium: One animal study reported that the protective effect of selenite in tumorigenesis was nullified by vitamin C. The chemopreventive action of selenomethionine, a form of selenium derived from foods, was not affected by the vitamin. Selenite may be reduced by vitamin C to a form that is not available for uptake by tissue.

Vitamin E: Vitamin C may regenerate or spare d-alpha-tocopherol. However, this is based on in vitro and animal studies. It is not yet known if this occurs in humans and, if it does, to what extent.

LABORATORY TESTS

Bilirubin assay: High intakes of vitamin C may cause falsely elevated bilirubin values.

Creatinine assay: Large intakes of vitamin C may cause falsely elevated urine and serum creatinine levels. However, this is not well documented.

Glucose assay: Large intakes of vitamin C may cause false positive glucose readings measured by copper reduction methods (e.g., Clinitest) and false negative glucose results as measured by the oxidase methods (e.g., Clinistix and Test-Tape).

Guaiac assay for occult blood: Intakes of vitamin C greater than 1 gram daily may cause a false negative guaiac test.

OVERDOSE

There are no reports of vitamin C overdose in the literature.

DOSAGE AND ADMINISTRATION

A dose of 200 milligrams daily is almost enough to maximize plasma and lymphocyte levels. Doses of vitamin C vary from those equivalent to the RDAs up to 5 to 10 grams daily and, in some, even higher. Typical doses used range from 500 milligrams to 2 grams daily. Some increase their dose to 4 to 5 grams daily when coming down with a cold. Such doses may have antihistaminic-like action. A dose of vitamin C of 5 grams daily for 4 weeks was found to significantly inhibit Helicobacter pylori in one report. Although a dose of 200 milligrams daily is almost enough to maximize plasma and lymphocyte levels, high doses may aid in detoxifying some carcinogens in the stomach prior to absorption of the vitamin.

Absorption of supplemental vitamin C is most efficient if spaced throughout the day or if taken in time-release form.

The DV (Daily Value) for vitamin C, which is used for determining percentage of nutrient daily values on nutritional supplement and food labels, is 60 mg. This is based on the U.S. RDA for vitamin C.

In the United States, the average intake of vitamin C is about 95 milligrams for women and 107 milligrams for men. Children between the ages of one to five consume about 83 milligrams daily.

The most recent (2,000) dietary reference intakes (DRI) for vitamin C are as follows:
### Vitamin C

#### Infants

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Adequate Intake (AI)</th>
<th>Tolerable Upper Intake Level (UL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-6 months</td>
<td>40 milligrams daily or 6mg/kg</td>
<td>ND</td>
</tr>
<tr>
<td>7-12 months</td>
<td>50 milligrams daily or 6mg/kg</td>
<td>ND</td>
</tr>
</tbody>
</table>

**Recommended Dietary Allowances (RDA)**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-3 years</td>
<td>15 mg daily</td>
</tr>
<tr>
<td>4-8 years</td>
<td>25 mg daily</td>
</tr>
<tr>
<td>9-13 years</td>
<td>45 mg daily</td>
</tr>
<tr>
<td>14-18 years</td>
<td>75 mg daily</td>
</tr>
<tr>
<td>19-30 years</td>
<td>90 mg daily</td>
</tr>
<tr>
<td>31-50 years</td>
<td>90 mg daily</td>
</tr>
<tr>
<td>51-70 years</td>
<td>90 mg daily</td>
</tr>
<tr>
<td>Older than 70 years</td>
<td>90 mg daily</td>
</tr>
<tr>
<td>Women 19-30 years</td>
<td>75 mg daily</td>
</tr>
<tr>
<td>31-50 years</td>
<td>75 mg daily</td>
</tr>
<tr>
<td>51-70 years</td>
<td>75 mg daily</td>
</tr>
<tr>
<td>Older than 70 years</td>
<td>75 mg daily</td>
</tr>
<tr>
<td>Pregnancy 14-18 years</td>
<td>80 mg daily</td>
</tr>
<tr>
<td>19-30 years</td>
<td>85 mg daily</td>
</tr>
<tr>
<td>31-50 years</td>
<td>85 mg daily</td>
</tr>
<tr>
<td>Lactation 14-18 years</td>
<td>115 mg daily</td>
</tr>
<tr>
<td>19-30 years</td>
<td>120 mg daily</td>
</tr>
<tr>
<td>31-50 years</td>
<td>120 mg daily</td>
</tr>
<tr>
<td>Smokers Men</td>
<td>125 mg daily</td>
</tr>
<tr>
<td>Women</td>
<td>110 mg daily</td>
</tr>
</tbody>
</table>

**LOAEL (Lowest-Observed-Adverse-Effect Level)**

- 3 grams daily has been established for vitamin C for adults. Based on this LOAEL, a Tolerable Upper Level Intake (UL) for the vitamin has been set at 2 grams daily for men and women 19 years and older.

### Literature

- Duconge J, Miranda-Massari JR, Gonzalez MJ, et al. Pharmacokinetics of vitamin C: insights into the oral and


Zinc

DESCRIPTION
Zinc is an essential element in human and animal nutrition with a wide range of biological roles. Zinc plays catalytic, structural or regulatory roles in the more than 200 zinc metalloenzymes that have been identified in biological systems. These enzymes are involved in nucleic acid and protein metabolism and the production of energy, among other things. Zinc plays a structural role in the formation of the so-called zinc fingers. Zinc fingers are exploited by transcription factors for interacting with DNA and regulating the activity of genes. Another structural role of zinc is in the maintenance of the integrity of biological membranes resulting in their protection against oxidative injury, among other things.

Zinc is a metallic element with atomic number 30 and an atomic weight of 65.37 daltons. Its atomic symbol is Zn. Zinc exists under physiological conditions in the divalent state. The adult body contains about 1.5 to 2.5 grams of zinc. It is present in all organs, tissues, fluids and secretions. Approximately 90% of total body zinc is found in skeletal muscle and bone. Over 95% of total body zinc is bound to proteins within cells and cell membranes. Plasma contains only 0.1% of total body zinc. Most of the zinc (75% to 88%) in blood is found in the red blood cell zinc metalloenzyme carbonic anhydrase. In the plasma, approximately 18% of zinc is bound to alpha-2-macroglobulin, 80% to albumin and 2% to such proteins as transferrin and ceruloplasmin.

Physiologically, zinc is vital for growth and development, sexual maturation and reproduction, dark vision adaptation, olfactory and gustatory activity, insulin storage and release and for a variety of host immune defenses, among other things. Zinc deficiency can result in growth retardation, immune dysfunction, increased incidence of infections, hypogonadism, oligospermia, anorexia, diarrhea, weight loss, delayed wound healing, neural tube defects of the fetus, increased risk for abortion, alopecia, mental lethargy and skin changes.

Moderate to severe zinc deficiency is rare in industrialized countries. However, it is highly prevalent in developing countries. Many, however, are at risk for mild zinc deficiency in industrialized countries. Several diseases and situations predispose to zinc deficiency, including the autosomal recessive disease acrodermatitis enteropathica, alcoholism, malabsorption, thermal burns, total parenteral nutrition (TPN) without zinc supplementation and certain drugs, such as diuretics, penicillamine, sodium valproate and ethambutol. Zinc intake in many of the elderly may be suboptimal and, if compounded with certain drugs and diseases, can lead to mild or even moderate zinc deficiency.

Zinc acetate is an FDA-approved orphan drug for the treatment of the copper-overload disorder Wilson’s disease.
ACTIONS AND PHARMACOLOGY

ACTIONS
Zinc may have immunomodulatory activity. It may also have antioxidant activity. Zinc has putative antiviral, fertility-enhancing and retinoprotective activities.

MECHANISM OF ACTION
Zinc is required for a number of immune functions, including T-lymphocyte activity. Zinc deficiency results in thymic involution, decreased proliferative T-lymphocyte response to phytohemagglutinin (PHA), decreased cytotoxic T-lymphocyte activity, depressed helper lymphocyte function, depressed natural killer cell activity, depressed macrophage function (phagocytosis), depressed neutrophil functions (respiratory burst, chemotaxis) and depressed antibody production. Zinc supplementation can restore impaired immune function in those with zinc deficiency, as found in malabsorption syndromes and acrodermatitis enteropathica.

There is little evidence that zinc supplementation will enhance immune responses in those who are not zinc deficient. High doses of zinc may even be immunosuppressive. Zinc supplementation may improve immune function in healthy elderly individuals who are marginally zinc deficient.

The mechanism underlying the immune effects of zinc is not fully understood. Some of these effects may be accounted for by zinc’s membrane-stabilization effect. This could affect signaling processes involved in cell-mediated immunity. Zinc is known to be involved in such signaling processes. Zinc may also influence gene expression by structural stabilization of different immunological transcription factors. Zinc ions can induce blast formation of human peripheral blood monocytes (PBMCs). In PBMCs, zinc induces cytokines, including interleukin (IL)-1, IL-6 and tumor necrosis factor (TNF)-alpha. Cytokine induction by zinc is caused by a direct interaction of zinc with monocytes. The stimulation of zinc by T-lymphocytes appears to occur via monocyte released IL-1 and cell-cell contact. High zinc concentrations inhibit T-lymphocyte proliferation by blocking the IL-1 type 1 receptor-associated kinase. T-lymphocyte activation appears to be delicately regulated by zinc concentrations.

Zinc may have secondary antioxidant activity. Zinc does not have redox activity under physiological conditions. Zinc may influence membrane structure by its ability to stabilize thiol groups and phospholipids. It may also occupy sites that might otherwise contain redox active metals such as iron. These effects may protect membranes against oxidative damage. Zinc also comprises the structure of copper/zinc-superoxide dismutase (Cu/Zn-SOD). Zinc plays a structural role in Cu/Zn-SOD. Zinc may also have antioxidant activity via its association with the copper-binding protein metallothionein.

The role of zinc gluconate in the management of the common cold remains controversial (see Research Summary). The mechanisms proposed for zinc’s effects on the duration of colds are inhibition by zinc of the replication of rhinoviruses and/or inhibition of virus entry into cells. Zinc ions, however, have only modest nonselective inhibitory effects for rhinoviruses in vitro.

Zinc is involved in sperm formation and testosterone metabolism. Zinc deficiency results in oligosperma. There is little evidence that zinc supplementation affects sperm production in those who are not zinc deficient.

The mechanism of the putative effect of zinc in age-related macular degeneration (ARMD) is unknown.

PHARMACOKINETICS
The efficiency of absorption (fractional absorption) of a zinc salt on an empty stomach ranges from 40% to 90%. The fractional absorption of zinc with food appears to be lower. Zinc-histidine, zinc-methionine and zinc-cysteine complexes appear to be more efficiently absorbed than other zinc supplementary forms. Zinc is absorbed all along the small intestine. Most ingested zinc appears to be absorbed from the jejunum. Zinc uptake across the brush border appears to occur by both a saturable barrier-mediated mechanism and a nonsaturable nonmediated mechanism. The exact mechanism of zinc transport into the enterocytes remains unclear. Zinc transporters have been identified in animal models. Once zinc is within the enterocyte, it can be used for zinc-dependent processes, become bound to metallothionein and held within the enterocyte or pass through the cell. Transport of zinc across the serosal membrane is carrier mediated and energy dependent.

Zinc is transported to the liver via the portal circulation. A fraction of zinc is extracted by the hepatocytes, and the remaining zinc is transported to the various cells of the body via the systemic circulation. Zinc is transported in the plasma bound to albumin (about 80%), alpha-2-macroglobulin (about 18%) and to such proteins as transferrin and ceruloplasmin (about 2%). The major route of zinc excretion is via the gastrointestinal tract. Fecal zinc excretion is comprised of unabsorbed zinc and zinc derived from biliary, pancreatic, and gastrointestinal secretions and zinc from sloughing of mucosal cells.

Much of the pharmacokinetics of zinc in humans is unknown. Research is ongoing.
INDICATIONS AND USAGE
Even borderline zinc deficiency or disturbances in zinc metabolism can have profound adverse health effects. Those at greatest risk of such deficiencies and disturbances include infants, children, the elderly and pregnant women. Due to conditions that can limit the bioavailability of zinc, even when there is adequate zinc intake, zinc deficiency may affect still larger populations.

Among diseases and conditions associated with zinc deficiency are alcoholism, malabsorption syndromes, acrodermatitis enteropathica, anorexia nervosa, thermal burns and total parenteral nutrition (TPN) without zinc supplementation. Supplemental zinc may be helpful in some of the foregoing, in some conditions of immune impairment, in some complications of pregnancy, in the prevention of some cases of fetal neural tube defects, diarrhea, oligospermia, delayed wound healing and some cognitive disorders. It may also help protect against some inflammatory conditions.

Some claim that zinc is neuroprotective, others that it is neurotoxic in some circumstances. Some have suggested it might be useful in depression, and some others have proposed that it might be used as an antiaging substance. Mixed results are reported in the use of zinc in childhood pneumonia.

Widely publicized claims that zinc is efficacious in preventing and ameliorating symptoms of the common cold are supported by some studies but not by others. There is the suggestion in some experimental research that zinc might have some anticarcinogenic effects. There is little evidence that zinc is helpful in diabetes. Topical zinc is useful in treating some skin conditions. Claims that it can prevent or reverse baldness are unsubstantiated except in some cases of severe zinc deficiency. It has no effect on typical male pattern baldness. It may be useful in dysgeusia (taste disorder) in those who are zinc deficient. There is growing evidence that zinc might be helpful in preventing age-related macular degeneration.

RESEARCH SUMMARY
Zinc deficiency has been shown to impair immunity in many ways. It decreases T- and B-lymphocyte function and diminishes proliferative responses to mitogens. It also reduces the biological activity of many cytokines. Zinc deficiency has been shown to impair placental transport of antibodies from mother to fetus. Even mild zinc deficiency has been shown to produce an imbalance between cell-mediated and humoral immunity. Zinc supplementation has reversed many of these and other immune deficits in several in vitro, animal and human studies.

Supplementation with zinc reduced the incidence of childhood pneumonia by 41% and incidence of diarrhea in children by 25%, according to the findings of a review of ten randomized, controlled studies in the developing world. Zinc was found, in this review analysis, to be more effective than any other treatment for childhood pneumonia and was said to equal most other effective interventives for diarrhea in these populations. The diarrheas studied were related to diminished immune competence and high rates of exposure to infectious diseases. The significance of these findings is underscored by the fact that respiratory infections, and pneumonia in particular, are the cause of approximately one-third of all deaths among children in developing countries.

Many healthy elderly individuals and even more unhealthy elderly have marginal zinc deficiencies. There is both clinical and experimental evidence of impaired T-lymphocyte function, with associated increases in morbidity and mortality due to infectious diseases, among the elderly. Zinc deficiency has been shown to play a key role in this situation. Zinc supplementation in the elderly has produced mixed results with respect to immune restoration. Many researchers agree, however, that some of the negative results are probably due to the heterogeneity of elderly populations with respect to immune response, and most call for better-designed studies to bring hitherto ambiguous data into sharper focus.

Disturbances in metabolism, as well as zinc deficiency, have been associated with some inflammatory conditions, including some inflammatory bowel diseases and rheumatoid arthritis. The use of supplemental zinc in gastrointestinal inflammation, however, is highly experimental and is not without peril since inappropriate or uncontrolled administration can exacerbate, rather than ameliorate, some of these conditions. In some circumstances, however, supplemental zinc has enhanced the mucosal capacity of the small bowel to absorb water and electrolytes, thus easing inflammation. There is also some experimental evidence that zinc can stimulate tissue repair in some ulcer conditions.

There is some preliminary clinical evidence that supplemental zinc can produce benefit in some with rheumatoid arthritis. Diminished plasma zinc has been reported in some with this disease. Zinc has demonstrated an ability to inhibit mixed lymphocyte reaction in some of these subjects. Some researchers have suggested that further research is warranted to see if zinc might be a useful new therapy in T-cell-mediated auto-immune and graft-versus-host diseases.

One review author has presented evidence that zinc can be neurotoxic in some experimental circumstances and neuroprotective in others. The author warned that "there is a large and growing body of evidence showing that after CNS injury, large quantities of free zinc can be released, not just from pre-synaptic vesicles but also from metalloproteins and
from mitochondrial zinc pools, resulting in neuronal damage and death.” Some in vitro work has shown neurotoxic zinc effects, and some in vivo studies have shown free zinc accumulation reportedly leading directly to neuronal death after ischemia, traumatic brain injury and seizure. And there is some, albeit inconsistent, data suggesting that zinc chelators may protect neurons after injury. At the same time, after ischemia, traumatic brain injury and seizure. And there is some, albeit inconsistent, data suggesting that zinc accumulation reportedly leading directly to neuronal death increases significantly in humans. Hence the reviewer stated that “while these data make it clear that systemic zinc deficiency after CNS injury should be avoided, our understanding of the role of free zinc in neuronal death raises the question of whether clinicians should be treating brain-injured patients with supplemental zinc.”

This issue was tested in a rat model of traumatic brain injury. Dietary supplementation with zinc subsequent to the induced brain trauma did not have deleterious effects, but the researchers cautioned that in patients with severe traumatic brain injury zinc supplementation would necessarily be administered parenterally with, potentially, significantly different effects. Another study provided at least some reassurance in this context: brain injured human adults received intravenous zinc for 15 days beginning within 72 hours of injury; three weeks after treatment began no adverse effects were observed, and, in fact, within two weeks after injury, those receiving zinc compared to those who did not receive it had improved recovery scores on the Glasgow Coma Scale. In another study, however, zinc chloride administered intraperitoneally 30 minutes prior to embolization of the middle cerebral artery in adult male rats resulted in increased infarct size and diminished behavioral outcomes, compared with other agents tested. Both studies used the same zinc form and dose. But the methods used to induce transient ischemia and reperfusion were different. Clearly more research needs to be done to try to further clarify the issues raised in these conflicting studies.

A group of reviewers examined data they said might indicate a role for zinc in treating depression. They presented evidence indicating that zinc deprivation influences brain homeostasis, mental function and susceptibility to epileptic convulsions. They also pointed to recent rat studies showing that chronic treatment with antidepressants and electroconvulsive shock therapy induces increased brain concentrations of zinc. Zinc supplementation has produced antidepressant-like effects in various animal depression models. The activity of some antidepressants was said to be enhanced when used in combination with zinc. There have been some reports that depression in humans is associated with lower serum zinc concentrations. At least one such inquiry, however, failed to find such an association. A preliminary clinical trial found some benefit from zinc supplementation in depressed individuals. More research is needed and warranted.

Another group of researchers, surveying a broad range of zinc data, recently concluded that zinc may have general antiaging properties: “An overall estimation of all experimental and clinical observations on the biological role of zinc seems to lead us to the conclusion that zinc supply may be useful in reducing infection relapse and in restoring immune efficiency in ageing and in preventing age-related degenerative disease.” However, they cautioned that it is far from being the ideal antiaging substance since there is also the potential for “acute and chronic zinc poisoning.”

Diminished zinc status has been associated with HIV disease and higher incidence of opportunistic infections. Zinc supplementation has produced higher CD4+ lymphocyte cell counts and reduced incidence of bacterial infections among patients with HIV disease in one study.

In a double-blind study, subjects were randomized to receive zinc lozenges containing 13.3 milligrams of zinc every two hours while awake for as long as they had symptoms of the common cold. Subjects were enrolled within 24 hours of first reporting cold symptoms. Median time to complete resolution of cold symptoms was 4.4 days in those supplemented with zinc, compared with 7.6 days in those receiving placebo. Patients dissolved the lozenges in their mouths, rather than immediately swallowing them.

A recent review of studies found findings similar to those reported above in three additional studies. Four other studies, however, found no benefit from zinc in shortening duration of cold symptoms. In one of the other positive studies, zinc supplementation reduced duration of symptoms by 42%, compared with placebo, when initiated on the first day of symptoms. When withheld until the second day, zinc reduced cold duration by 26%, compared with placebo.

Some have challenged the validity of the four studies that found no zinc effect on the basis of poor bioavailability of the zinc lozenge preparations, either due to a proposed failure of the lozenge formulations to provide adequate amounts of free zinc ions to the saliva and oral tissues or due to doses of zinc in the lozenge that were below a possible therapeutic threshold. On the other hand, some have also argued that there were significant methodological flaws in some of the positive studies. A recent review of the zinc/cold data evaluated 14 randomized, placebo-controlled studies. Half reported positive effects; half reported no effect. Of the four studies the review authors considered the most rigorous and best-designed, three found no effect, and one reported a positive effect—but it used a nasal gel as the delivery form. Whether zinc is truly effective against colds remains an unresolved issue.
A group of researchers has recently concluded that supplemental zinc has been shown to reduce the incidence of childhood pneumonia. Some studies in which it has been used as an adjunct to antibiotic therapy have yielded mixed results. A recent trial suggested that supplemental zinc might actually be detrimental in some cases of childhood pneumonia. Again, the picture is unclear, and more research is required.

Zinc supplementation has reversed some of the signs of anorexia nervosa, including weight loss, in some women. Weight has increased in some zinc-supplemented women with this condition, and menstruation has been restored in some supplemented with zinc.

Zinc supplementation has overcome some forms of both female and male infertility in those who are zinc deficient. Zinc is essential for proper formation and maturation of spermatozoa.

Zinc plays many roles in pregnancy, and disturbances in zinc metabolism, as well as zinc deficiency, can have serious adverse effects on the course of pregnancy and upon the growth of the fetus and newborn. Zinc deficiency can be teratogenic, producing neural tube defects. Zinc is also very important to the newborn when breast milk may be its only source of zinc (during the first few months of life). Premature infants may be at even greater risk of zinc deficiency. Impaired disease resistance and diminished vaccine efficacy in infants may result from zinc deficiency at this stage. Some studies have shown that giving 15 milligrams of zinc daily to breast-feeding mothers produced more weight gain in their babies than in the babies of unsupplemented mothers. Zinc supplementation in infants not breast fed has also shown benefits. Zinc supplementation has also shown benefit in regulating and promoting proper growth in some groups of young children with non-organic failure to thrive.

There is some evidence that zinc can promote and accelerate wound healing in some circumstances. There is very preliminary experimental evidence that it may have some protective effects against prostate cancer and some equally preliminary data suggesting that it might enhance neuropsychological performance in children, most likely those with zinc deficiencies.

There was an early report that 100 milligrams of zinc twice a day with meals significantly reduced visual loss in subjects with macular degeneration. Subsequently, in a much larger study organized by the National Eye Institute, a combination of zinc, vitamin E, beta-carotene and vitamin C reportedly reduced the risk of developing age-related macular degeneration and prevented blindness in a high-risk group of elderly subjects. Mortality was also increased in the supplemented group.

CONTRAINDICATIONS, PRECAUTIONS, ADVERSE REACTIONS

CONTRAINDICATIONS
Zinc is contraindicated in those who are hypersensitive to any component of a zinc-containing supplement.

PRECAUTIONS
Pregnant women and nursing mothers should avoid zinc doses higher than RDA amounts (15 milligrams/day for pregnant women, 19 mg/day for lactating women during the first six months and 16 mg/day for lactating women during the second six months).

ADVERSE REACTIONS
Doses of zinc up to 30 milligrams daily are generally well tolerated. Higher doses may cause adverse reactions. The most common adverse reactions are gastrointestinal and include nausea, vomiting and gastrointestinal discomfort. Other adverse reactions include a metallic taste, headache and drowsiness. There are some reports of decreased HDL-cholesterol in those taking high doses of zinc. Chronic intake of high doses of zinc can lead to copper deficiency and hypochromic, microcytic anemia secondary to zinc-induced copper deficiency.

High doses of zinc may be immunosuppressive.

INTERACTIONS

DRUGS
Bisphosphonates (alendronate, etidronate, risedronate): Concomitant intake of a bisphosphonate and zinc may decrease the absorption of both the bisphosphonate and zinc.

Quinolones (ciprofloxacin, gatifloxacin, levofloxacin, lomefloxacin, moxifloxacin, norfloxacin, ofloxacin, sparfloxacin, trovafloxacin): Concomitant intake of a quinolone and zinc may decrease the absorption of both the quinolone and zinc.

Penicillamine: Concomitant intake of penicillamine and zinc may depress absorption of zinc.

Tetracyclines (doxycycline, monocycline, tetracycline): Concomitant intake of a tetracycline and zinc may decrease the absorption of both the tetracycline and zinc.

Copper: Concomitant intake of copper and zinc may depress the absorption of copper. Intake of large doses of zinc can negatively affect the copper status of the body. This is the basis for the use of high doses of zinc for the treatment of Wilson's disease. It is thought that high intakes of zinc induce synthesis of the copper-binding protein metallothio-
nine in the gastrointestinal mucosal cells. Metallothionine can sequester copper. This makes copper unavailable for copper absorption.

**L-cysteine:** Concomitant intake of L-cysteine and zinc may enhance the absorption of zinc.

**L-histidine:** Concomitant intake of L-histidine and zinc may enhance the absorption of zinc.

**Inositol Hexaphosphate:** Concomitant intake of inositol hexaphosphate and zinc may depress the absorption of zinc.

**Iron:** Concomitant intake of iron and zinc may depress the absorption of both iron and zinc.

**L-methionine:** Concomitant intake of L-methionine and zinc may enhance the absorption of zinc.

**N-acetyl-L-cysteine (NAC):** Concomitant intake of NAC and zinc may enhance the absorption of zinc.

**Phosphate Salts:** Concomitant administration of zinc and phosphate salts may decrease the absorption of zinc.

**FOODS**

**Caffeine:** Concomitant intake of coffee, caffeinated beverages or caffeine and zinc may depress the absorption of zinc.

**Cysteine-containing Proteins:** Foods rich in cysteine-containing proteins (e.g., animal muscle tissue) may increase the absorption of zinc if ingested concomitantly.

**Oxalic Acid:** Concomitant intake of zinc with foods rich in oxalic acid (spinach, sweet potatoes, rhubarb and beans) may depress the absorption of zinc.

**Phytic Acid:** Concomitant intake of zinc with foods rich in phytic acid (unleavened bread, raw beans, seeds, nuts and grains and soy isolates) may depress the absorption of zinc.

**Tea:** Concomitant intake of tea (tannins) and zinc may cause decreased absorption of zinc.

**OVERDOSAGE**

There are no reports of overdosage from use of zinc supplements.

**DOSAGE AND ADMINISTRATION**

There are several zinc supplementary forms. These include zinc gluconate, zinc oxide, zinc aspartate, zinc picolinate, zinc citrate, zinc monomethionine and zinc histidine. Zinc supplements are available in stand-alone or in combination products. A typical dose of zinc is about 15 milligrams (as elemental zinc) daily.

The Food and Nutrition Board of the Institute of Medicine of the National Academy of Sciences has recommended the following Dietary Reference Intakes (DRI) for zinc:

<table>
<thead>
<tr>
<th>Age/Condition</th>
<th>Recommended Daily Allowance (RDA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-6 months</td>
<td>2 mg/day (AI, adequate intake)</td>
</tr>
<tr>
<td>7-12 months</td>
<td>3 mg/day</td>
</tr>
<tr>
<td>Children</td>
<td></td>
</tr>
<tr>
<td>1-3 years</td>
<td>3 mg/day</td>
</tr>
<tr>
<td>4-8 years</td>
<td>5 mg/day</td>
</tr>
<tr>
<td>Boys</td>
<td></td>
</tr>
<tr>
<td>9-13 years</td>
<td>8 mg/day</td>
</tr>
<tr>
<td>14-18 years</td>
<td>11 mg/day</td>
</tr>
<tr>
<td>Girls</td>
<td></td>
</tr>
<tr>
<td>9-13 years</td>
<td>8 mg/day</td>
</tr>
<tr>
<td>14-18 years</td>
<td>9 mg/day</td>
</tr>
<tr>
<td>Men</td>
<td></td>
</tr>
<tr>
<td>19-30 years</td>
<td>11 mg/day</td>
</tr>
<tr>
<td>31-50 years</td>
<td>11 mg/day</td>
</tr>
<tr>
<td>51-70 years</td>
<td>11 mg/day</td>
</tr>
<tr>
<td>Older than 70 years</td>
<td>11 mg/day</td>
</tr>
<tr>
<td>Women</td>
<td></td>
</tr>
<tr>
<td>19-30 years</td>
<td>8 mg/day</td>
</tr>
<tr>
<td>31-50 years</td>
<td>8 mg/day</td>
</tr>
<tr>
<td>51-70 years</td>
<td>8 mg/day</td>
</tr>
<tr>
<td>Older than 70 years</td>
<td>8 mg/day</td>
</tr>
<tr>
<td>Pregnancy</td>
<td></td>
</tr>
<tr>
<td>14-18 years</td>
<td>12 mg/day</td>
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<tr>
<td>19-30 years</td>
<td>11 mg/day</td>
</tr>
<tr>
<td>31-50 years</td>
<td>11 mg/day</td>
</tr>
<tr>
<td>Lactation</td>
<td></td>
</tr>
<tr>
<td>14-18 years</td>
<td>13 mg/day</td>
</tr>
<tr>
<td>19-30 years</td>
<td>12 mg/day</td>
</tr>
<tr>
<td>31-50 years</td>
<td>12 mg/day</td>
</tr>
</tbody>
</table>

The following summarizes the Tolerable Upper Intake Level (UL) for various age groups and conditions:

<table>
<thead>
<tr>
<th>Age/Condition</th>
<th>Recommended Daily Allowance (UL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants</td>
<td>4 mg/day</td>
</tr>
<tr>
<td>0-6 months</td>
<td>5 mg/day</td>
</tr>
<tr>
<td>7-12 months</td>
<td></td>
</tr>
<tr>
<td>Children</td>
<td>7 mg/day</td>
</tr>
<tr>
<td>1-3 years</td>
<td>12 mg/day</td>
</tr>
<tr>
<td>4-8 years</td>
<td>23 mg/day</td>
</tr>
<tr>
<td>9-13 years</td>
<td></td>
</tr>
<tr>
<td>Adolescents</td>
<td>34 mg/day</td>
</tr>
<tr>
<td>14-18 years</td>
<td></td>
</tr>
</tbody>
</table>
Adults
19 years and older 40 mg/day

Pregnancy
14-18 years 34 mg/day
19 years and older 40 mg/day

Lactation
14-18 years 34 mg/day
19 years and older 40 mg/day

The DV (Daily Value) for zinc, which is used for determining percentage of nutrient daily values on nutritional supplement and food labels, is 15 mg. The basis for the DV for zinc is the 1973 U.S. RDA.

LITERATURE


Mocchegiani E; Zincage Consortium. Zinc, metallothioneins, longevity: effect of zinc supplementation on antioxidant
Zinc L-Carnosine

DESCRIPTION

Zinc L-carnosine is a chelate of divalent zinc and the dipeptide L-carnosine. L-carnosine (see Carnosine) is comprised of the nonprotein amino acid beta-alanine (see Beta-alanine) and the protein amino acid L-histidine.

Zinc L-carnosine was synthesized by the Japanese in the late 1980s. It was first known as Z-103 and later on as polaprezinc. The idea for the synthesis of zinc L-carnosine came from the knowledge that L-carnosine was reported to increase granulation tissue and accelerate gastric healing in rats, and that zinc had been reported to have protective action against various experimental gastric lesions and also had been reported to possess antifulcer action in clinical studies. The thinking was that the combination of the beneficial effects of zinc and L-carnosine under the chemical roof of one molecule would make for a novel and potent antifulcer agent. Japanese researchers found that the zinc L-carnosine complex did exhibit marked antifulcer activity against various experimental models of gastric ulcers and duodenal ulcers by acting directly on the gastric and intestinal mucosa. However, even during the early days of zinc L-carnosine research, it was already demonstrated to have other activities, such as inhibition of bone resorption in experimental animals. Recently, zinc L-carnosine entered the dietary supplement market in the United States.

Zinc L-carnosine is described chemically as 2-[(3-azanylidene)(3H-imidazol-4-yl)propanoate. It is also known as polaprezinc, zinc carnosine, l3-alanyl-L-histidinato zinc, and catena-(S)-[N-[1-oxidopropylidene)amino]-2-{[(3-azanylidene)(3H-imidazol-4-yl)propanoate. Originally known as Z-103, zinc L-carnosine was demonstrated to be much more active against gastric ulceration in rats than various other Zn(II) complexes. Zinc D-carnosine was found to have little or no activity. Spectroscopic data indicated that the zinc ions coordinate with L-carnosine to form a quadridentate 1:1 complex of...
polymeric nature in order to maintain low strain of the chelate rings. Small amounts of zinc L-carnosine may be found in muscle and nervous tissue. (Carnosine in muscle and nervous tissue may form chelates with zinc, copper and iron.)

Zinc L-carnosine’s empirical formula is \((\text{C}_9\text{H}_{12}\text{N}_4\text{O}_3\text{Zn})_n\), its molecular weight is 288.62, and its CAS Registry Number is 107667-60-7. It is insoluble in water and common organic solvents, but does dissolve in acid, including stomach acid.

Zinc L-carnosine is represented by the following chemical structure.

![Zinc L-carnosine structure]

**ACTIONS AND PHARMACOLOGY**

**ACTIONS**

Zinc L-carnosine has antiulcer, antigastritis and mucosal protective activities. It may also have bone-protective and hepatoprotective activities.

**MECHANISM OF ACTION**

**Antiulcer activity:** In an early study of zinc L-carnosine and peptic ulcer disease, it was found that the agent prevented ethanol-induced gastric mucosal damage in rats through increases in the activities of the gastric mucosal antioxidant enzymes superoxide dismutase (SOD) and glutathione peroxidase (GSH-px). Zinc L-carnosine also inhibited the increase in thiobarbituric acid reactive substances (TBARS) in gastric mucosa injured by the ethanol. (TBARS is a measure of oxidative stress.) The study authors concluded that the protective mechanism of zinc L-carnosine against gastric ulceration was due, at least in part, to the scavenging of oxygen-derived free radicals via increases in the synthesis of SOD and GSH-px in the gastric mucosa, induced by zinc L-carnosine.

The antiulcer pharmacological effects of zinc L-carnosine on indomethacin-induced gastric lesions and acetic acid-induced gastric ulcers, were found to be significantly greater than those of either of its components, L-carnosine and divalent zinc, or a mixture of the two. In a study with rats, it was determined that zinc L-carnosine, which acts directly in mucosal lesions, was retained in the stomach much longer and adhered to the ulcerous sites more strongly than did divalent zinc or L-carnosine. The characteristics of the compound were thought to arise from its much lower solubility when compared to the high solubility of divalent zinc forms, such as zinc sulfate or L-carnosine.

In a study with primary monolayer cultures of rat gastric fundic mucosa, it was demonstrated that zinc L-carnosine protected gastric cells from oxidative stress caused by hydrogen peroxide and ethanol *in vitro*, that ethanol-induced cytotoxicity was linked with superoxide anion radical production from cells, and that zinc L-carnosine-induced protection against ethanol seemed to be due, at least in part, to the scavenging of reactive oxygen species (ROS). The authors of the study concluded that zinc L-carnosine worked via an antioxidant mechanism and directly protected gastric mucosal cells from noxious agents via its antioxidant properties in *in vitro*, independently of microcirculatory and neural or hormonal factors.

The antiulcer and mucocytotoxic protective effects of zinc L-carnosine may be explained, in part, by its antioxidant properties, as well as its stimulative effect on mucus secretion and its membrane-stabilizing effect. However, this does not completely explain the mechanism of action of its antiulcer activity. In a study using gastric epithelial cells (MKN28, a cell line derived from moderately differentiated gastric carcinoma), it was reported that zinc L-carnosine suppressed interleukin-8 (IL-8) secretion induced by tumor necrosis factor-alpha (TNF-alpha) or interleukin-1 beta (IL-1beta) dose-dependently. IL-8 messenger RNA expression was also inhibited by zinc L-carnosine. Proinflammatory cytokine nuclear factor-kappaB (NF-kappaB) activation in response to TNF-alpha, IL-1beta, phorbol ester, and hydrogen peroxide, was downregulated by zinc L-carnosine. Further, Western blot analysis revealed inhibition of TNF-alpha-induced IkappaB-alpha phosphorylation in the presence of zinc L-carnosine.

Thus, an anti-inflammatory action, specifically the downregulation of proinflammatory cytokine-induced NF-kappaB activation and IL-8 expression in gastric epithelial cells, can be added to the list of zinc L-carnosine’s antiulcer mechanisms of action.

To add yet another mechanistic possibility, zinc L-carnosine was shown to inhibit indomethacin-induced apoptosis in the rat gastric epithelial cell line RGM1, a diploid and non-transformed epithelial cell line isolated from normal Wistar rat gastric mucosa. Pretreatment of the cells with zinc L-carnosine suppressed caspase-3 activation and subsequent apoptosis in the cells exposed to indomethacin, dose-dependently. Treatment of the cells with indomethacin did produce
ROS, but zinc L-carnosine did not scavenge ROS in the indomethacin-treated cells, ruling out an antioxidant mechanism of action. Thus, in this case, zinc L-carnosine inhibited apoptosis via inhibition of caspase-3 activation, not by antioxidant activity.

Zinc L-carnosine was reported to help in the healing of acute gastric lesions in diabetic rats. In this case, enhancement of mucosal insulin-like growth factor-1 (IGF-1) messenger RNA expression was thought to contribute to the effect. The effect of zinc L-carnosine on cellular proliferation was studied in human umbilical vein endothelial cells (HUVEC), human foreskin fibroblasts and guinea pig gastric mucosal cells. Zinc L-carnosine stimulated cellular proliferation in the HUVEC and the human foreskin fibroblasts, but did not stimulate proliferation in the guinea pig gastric mucosal cells. Stimulation of cellular proliferation was accompanied by increased IGF-1 messenger RNA levels. The authors of the study concluded that their results suggested that the promotion of wound healing by zinc L-carnosine was related to a proliferative effect on nonparenchymal cells, with zinc and IGF-1 being important for the action. Although divalent zinc in the form of zinc sulfate also demonstrated a proliferative effect, its action was much weaker than that of zinc L-carnosine.

The effects of the roles of inflammatory cytokines, neutrophil accumulation and lipid peroxidation in the protective effect of zinc L-carnosine against aspirin-induced gastric mucosal injury was examined in rats. Zinc L-carnosine dose-dependently inhibited the total gastric erosive area following aspirin administration, inhibited increases in thiobarbituric acid-reactive substances (TBARS), an index of lipid peroxidation, and inhibited tissue-associated myeloperoxidase activity. TBARS and myeloperoxidase activity are both markers of oxidative stress. In addition, zinc L-carnosine dose-dependently inhibited the aspirin-induced rise in the inflammatory cytokine tumor necrosis factor-alpha (TNF-alpha). This study suggested that the protective effects of zinc L-carnosine on aspirin-induced gastric mucosal injury may be attributed to its antioxidative and anti-inflammatory activities.

\textit{Helicobacter pylori} is a common cause of chronic gastritis and peptic ulcer disease. In \textit{H. pylori}-colonized gastric mucosa, activated neutrophils generate superoxide anion radicals and hydrogen peroxide. Myeloperoxidase in neutrophils catalyzes the oxidation of chloride by hydrogen peroxide to produce hypochlorous acid. The hypochlorous acid reacts with ammonia generated by \textit{H. pylori} to produce monochloramine. The monochloramine is reactive, toxic and causes gastric mucosal cell injury via damage to DNA. Zinc L-carnosine has been reported to inhibit \textit{H. pylori}-induced gastritis and DNA damage in Mongolian gerbils through its scavenging action against monochloramine.

The treatment of \textit{H. pylori} is a course of triple therapy, usually with the two antibiotics—amoxicillin and clarithromycin—and a proton pump inhibitor. In a clinical study, a seven-day course of triple therapy with amoxicillin, clarithromycin and lansoprazole was found to be effective in \textit{H. pylori} eradication, but the regimen was significantly improved by the addition of zinc L-carnosine.

Zinc L-carnosine has also been found to protect against colonic mucosal injury. A study investigated the effects of zinc L-carnosine on acetic acid-induced colonic mucosal injury in rats \textit{in vivo}. Zinc L-carnosine inhibited visible damage in the rat colonic mucosa and this was accompanied by a significant increase in the expression of heat shock protein 72 (HSP72) and suppression of nuclear factor-kappaB (NF-kappaB) activation in the colonic mucosa. Heat shock proteins protect cells against heat stress as well as other stressors. The authors of the study suggested that, based on the findings, zinc L-carnosine may be a novel treatment for inflammatory bowel disease. The mechanism of action of this effect is not completely understood, but continued research in this area is needed and warranted.

\textbf{Bone-protective activity:} Zinc L-carnosine has been reported to have possible antiosteoporosis and bone-sparing activities. However, the mechanism of action of these effects is unclear. In one study, prolonged administration of zinc L-carnosine to ovariectomized rats was found to prevent bone loss. In another study, using mouse marrow cultures, an inhibitory effect of zinc L-carnosine on parathyroid hormone (PTH)-stimulated osteoclast-like cell formation was reported. It was speculated that the zinc L-carnosine inhibition of the PTH-stimulated osteoclast-like cell formation was mediated via calcium-dependent activation of protein kinase C.

A small clinical pilot study of postmenopausal women with rheumatoid arthritis reported that zinc L-carnosine improved periarticular osteoporosis, probably through an increase in bone formation.

Zinc L-carnosine has been found to promote the differentiation of osteoblasts, to suppress the formation of osteoclasts and to prevent the progression of osteoporosis. These findings, if they can be verified, could have powerful applications to promote new bone formation, including periodontal bone regeneration. High quality randomized, double-blind, placebo-controlled clinical trials are very much needed and warranted in order to learn if zinc L-carnosine has any role to play in bone regeneration.

\textbf{Hepatoprotective activity:} Non-alcoholic steatohepatitis (NASH) is an increasingly common disorder, which may
have serious consequences. This has only recently been recognized. In some cases, it may lead to liver fibrosis, cirrhosis and even hepatocellular carcinoma. The pathogenesis of NASH is unclear. Although a similar condition can occur in people who abuse alcohol, NASH occurs in those who drink little or no alcohol.

The effects of zinc L-carnosine on the development of NASH was investigated in a mouse model of the disease. Zinc L-carnosine was demonstrated to reduce lipid peroxidation, to suppress messenger RNA expression of proinflammatory cytokines and to suppress the activation of hepatic stellate cells. (Stellate cell activation is the central event in hepatic fibrosis.) The results suggested that zinc L-carnosine attenuated fibrosis in NASH by reducing lipid peroxidation and inflammation, and, during a later phase, promoting fibrinolysis by inhibiting tissue inhibitors of metalloproteinase expression.

In a small clinical trial of patients with early liver cirrhosis, it was reported that those patients who received zinc L-carnosine demonstrated reduction in the activity of tissue inhibitors of metalloproteinase-1 as well as decreased levels of type IV collagen, a marker of fibrosis.

Further research in this area is needed and warranted.

A few studies on the effects of zinc L-carnosine have also been performed on patients with chronic hepatitis C infection. In one study, it was reported that zinc L-carnosine administration resulted in reduced hepatocyte injury as measured by the increase in serum transaminase enzyme levels in patients with hepatitis C who were on therapy with pegylated interferon alpha-2b and ribavirin. The mechanism of this effect was not clear. However, the authors of the study speculated that the effect of zinc L-carnosine had to do with its possible antioxidant activity.

In another study of patients with chronic hepatitis C infection, it was reported that those patients receiving zinc L-carnosine had reduced iron overload as determined by serum ferritin levels. Again, the mechanism of this effect was unclear.

PHARMACOKINETICS

There is very little on the pharmacokinetics (PK) of zinc L-carnosine in humans. Studies of the PK of zinc L-carnosine in rats show that, following ingestion, zinc L-carnosine slowly dissociates into its components, L-carnosine and divalent zinc. Zinc L-carnosine, which acts directly in mucosal lesions, is retained in the stomach much longer than other forms of divalent zinc and adheres to the mucosal lesions and ulcerous sites much more than do divalent zinc and L-carnosine themselves. The characteristics of the compound may arise from its much lower solubility when compared to the high solubility of divalent zinc, for example, in the form of zinc sulfate, and L-carnosine. One can think of zinc L-carnosine in this regard as a slow-release form of divalent zinc and L-carnosine.

In the rat studies, zinc was found to be efficiently absorbed from the small intestine. However, it is unclear how much zinc L-carnosine, if any, is transported into the body. It is known that following absorption, zinc is mainly bound to albumin and transported from the intestine to the liver via the portal system. Zinc was found mainly excreted in the feces; a small amount was found excreted in the urine. (See Zinc and L-carnosine for further information on the PK of zinc and of L-carnosine.)

INDICATIONS AND USAGE

Zinc L-carnosine is a one-to-one complex of a synthetic derivative of carnosine and zinc. It is marketed as a zinc supplement with claimed benefits for gastric health. It may help protect the liver against hepatitis C infection and other stressors. It could have some radioprotective effects.

RESEARCH SUMMARY

Polaprezinc (zinc L-carnosine), an anti-ulcer drug which is a chelate compound consisting of zinc and L-carnosine, has been used in a number of studies in which it demonstrates an ability to protect against gastric mucosal injury. It inhibited indomethacin-induced apoptosis in a rat gastric mucosal cell line in a dose-dependent manner, apparently by suppressing activation of caspase-3, which plays a role in cell death by cleaving cellular protein substrates. An antioxidant mode of action was not observed in this study, and the zinc, rather than the L-carnosine, was thought to be responsible for the caspase-3 inhibition. In another study, polaprezinc was shown to inhibit Helicobacter pylori-associated gastritis in gerbils. The authors believe the agent scavenged monochloramine, which has been associated with H. pylori-associated gastric mucosal injury. Rats administered zinc L-carnosine were protected against acetic-acid induced colonic mucosal injury in another study. The effect was attributed to induction of heat shock protein 72 and suppression of nuclear factor kappa B (NF-kB). The heat shock proteins are thought to have cytoprotective functions in the presence of various stressors. NF-kB is involved in inflammation. These authors concluded that zinc L-carnosine may have significant potential as a new therapeutic drug for inflammatory bowel disease.

More recently, a number of studies have suggested a possible role for zinc L-carnosine in the treatment of chronic hepatitis C infection. Human subjects with this disease were randomly administered 150 mg of polaprezinc daily for 48 weeks in combination with the drugs interferon and ribavirin and 300 mg of vitamin E and 600 mg of vitamin C daily or, in the
case of the controls, the same regimen devoid of the zinc L-carnosine supplement. Increase in transaminase was significantly prevented in those receiving the zinc L-carnosine, compared with controls. The authors of this study concluded that the zinc L-carnosine supplementation thus reduced hepatocyte injury during the treatment period and attributed this favorable effect to an antioxidative action.

In another recent study of 14 patients with hepatitis C-related chronic liver disease, subjects were given polaprezinc 225 mg/day for six months along with other medications. The zinc L-carnosine supplement was credited in this study with a significant decrease in iron overload, thought to have resulted from the supplement’s anti-inflammatory activity in the liver. The authors recommend zinc L-carnosine as a complementary therapy for hepatitis C-related chronic liver disease.

Also recently, another group of researchers has shown that polaprezinc attenuates liver fibrosis in a mouse model of non-alcoholic steatohepatitis. An inhibition of inflammation and lipid peroxidation was reported. Oral supplementation with polaprezinc for 24 weeks resulted in benefit to patients with early cirrhosis, again primarily due to hepatitis C infection, compared with controls.

The extent to which zinc L-carnosine supplementation can be liver-protective in healthy individuals is unknown. More research is needed and warranted.

Noting that polaprezinc has exhibited various antiapoptotic effects in the gut, researchers have recently examined the effects of this substance on radiation-induced apoptosis in rat jejunal crypt cells. Pretreatment with the agent significantly reduced the number of apoptotic cells. Whether this could be of benefit in ameliorating damage related, for example, to radiotherapy for pelvic malignancies demands further study.

CONTRAINDICATIONS, PRECAUTIONS, ADVERSE REACTIONS

CONTRAINDICATIONS

Zinc L-carnosine dietary supplements are contraindicated in those who are hypersensitive to any component of a zinc L-carnosine-containing supplement.

PRECAUTIONS

Those who wish to try a zinc L-carnosine supplement for a health condition should first discuss its use with his or her physician.

Because of the lack of long-term safety studies on zinc L-carnosine dietary supplements, pregnant women and nursing mothers should avoid their use.

ADVERSE REACTIONS

No reports.

INTERACTIONS

DRUGS

H2 blockers (cimetidine, ranitidine, famotidine): The combination of an H2 blocker and zinc L-carnosine may be more effective than when each agent is used alone.

Sucralfate: The combination of the cytoprotectant sucralfate and zinc L-carnosine may be more effective than when each agent is used alone.

NUTRITIONAL SUPPLEMENTS

No known interactions.

FOOD

No known interactions.

HERBS

No known interactions.

OVERDOSAGE

There are no reports of overdosage from use of zinc L-carnosine supplements.

DOSAGE AND ADMINISTRATION

Zinc L-carnosine supplements are available in strengths of 37.5 milligrams and 75 milligrams. Amounts used in most gastric ulcer studies were 75 milligrams twice daily. Doses higher than those recommended on the supplement label should not be exceeded.

LITERATURE


Miller OJ, O’Oowd A. Vascular smooth muscle actions of carnosine as its zinc complex are mediated by histamine H(1) and H(2) receptors. *Biochemistry (Mosc).* 2000;65(7):798-806.


