INDICATIONS AND USAGE

Claims are made that liver supplements improve fat metabolism, impart energy, help damaged tissues regenerate and protect the liver. There is no credible evidence to support any of these claims.

RESEARCH SUMMARY

There are no credible studies supporting the use of liver supplements.

CONTRAINDICATIONS, PRECAUTIONS, ADVERSE REACTIONS

CONTRAINDICATIONS

Liver hydrolysate and desiccated liver are contraindicated in those who are hypersensitive to any component of a liver hydrolysate- or desiccated liver-containing supplement.

PRECAUTIONS

Liver hydrolysate and desiccated liver supplements should be avoided by pregnant women, nursing mothers and children.

Those with hemochromatosis, sickle cell anemia, sideoblastic anemia and thalassemia should be extremely cautious in the use of liver hydrolysate and desiccated liver supplements.

Those who receive frequent blood transfusions and those with chronic liver failure should be extremely cautious in the use of liver hydrolysate and desiccated liver supplements.

The treatment of iron-deficiency anemia should be under the advice and supervision of a physician. Liver hydrolysate and desiccated liver are not standard treatments for iron-deficiency anemia.

ADVERSE REACTIONS

No reports.

INTERACTIONS

DRUGS

Heme iron is unlikely to have the types of drug interactions that iron salts do (see Iron).

NUTRITIONAL SUPPLEMENTS

Heme iron in liver hydrolysate and desiccated liver may be additive to the effects of iron supplements.

DOSAGE AND ADMINISTRATION

There are several forms of liver hydrolysate and desiccated liver that are marketed as nutritional supplements. There are no typical doses of these supplements.

LITERATURE

Fujisawa K. Therapeutic effects of liver hydrolysate preparation on chronic hepatitis: a double-blind, controlled study. *Asian Med J.* 1984; 26:497-526.

Ohbayashi A, Akioka T, Tasaki H. A study of effects of liver hydrolysate on hepatic circulation. *J Therapy.* 1972; 54:1582-1585.

Washizuka M, Hiraga Y, Furuichi H, et al. [Effect of liver hydrolysate on ethanol- and acetaldehyde- induced deficiencies]. [Article in Japanese]. *Nippon Yakurigaku Zasshi.* 1998; 111:117-125.

Lutein and Zeaxanthin

DESCRIPTION

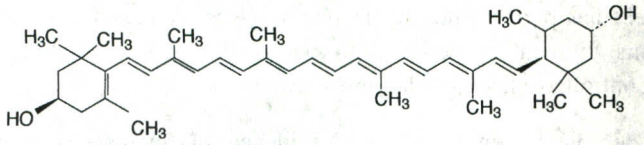
Lutein and zeaxanthin are members of the carotenoid family, a family best known for another one of its members, beta-carotene (see Beta-Carotene). They are natural fat-soluble yellowish pigments found in some plants, algae and photosynthetic bacteria. They serve as accessory light-gathering pigments and to protect these organisms against the toxic effects of ultra-violet radiation and oxygen. They also appear to protect humans against phototoxic damage. Lutein and zeaxanthin are found in the macula of the human retina, as well as the human crystalline lens. They are thought to play a role in protection against age-related macular degeneration (ARMD) and age-related cataract formation. They may also be protective against some forms of cancer. These two carotenoids are sometimes referred to as macular yellow, retinal carotenoids or macular pigment.

Food sources of lutein and zeaxanthin, include corn, egg yolks and green vegetables and fruits, such as broccoli, green beans, green peas, brussels sprouts, cabbage, kale, collard greens, spinach, lettuce, kiwi and honeydew. Lutein and zeaxanthin are also found in nettles, algae and the petals of many yellow flowers. In green vegetables, fruits and egg yolk, lutein and zeaxanthin exist in non-esterified forms. They also occur in plants in the form of mono-or diesters of fatty acids. For example, lutein and zeaxanthin dipalmitates, dimyristates and monomyristates are found in the petals of the marigold flower (*Tagetes erecta*). Many of the marketed lutein nutritional supplements contain lutein esters, with much smaller amounts of zeaxanthin esters, which are derived from the dried petals of marigold flowers.

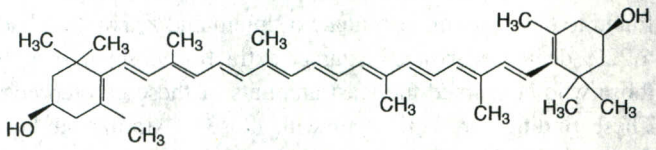
Lutein dipalmitate is found in the plant *Helenium autumnale* L. Compositae. It is also known as helenien and it is used in France for the treatment of visual disorders. Zeaxanthin in its fatty acid ester forms, is the principal carotenoid found in the plant *Lycium chinese* Mill. *Lycium chinese* Mill, also known as Chinese boxthorn, is used in traditional Chinese medicine for the treatment of a number of disorders, including visual problems.

Lutein and zeaxanthin belong to the xanthophyll class of carotenoids, also known as oxycarotenoids. The xanthophylls, which in addition to lutein and zeaxanthin, include alpha-and beta-cryptoxanthin, contain hydroxyl groups. This makes them more polar than carotenoids, such as beta-

carotene and lycopene, which do not contain oxygen. Although lutein and zeaxanthin have identical chemical formulas and are isomers, they are not stereoisomers, as is sometimes believed. They are both polyisoprenoids containing 40 carbon atoms and cyclic structures at each end of their conjugated chains. Also, they both occur naturally as *all-trans* (*all-E*) geometric isomers. The principal difference between them is in the location of a double bond in one of the end rings. This difference gives lutein three chiral centers rather than the two that are found in zeaxanthin. The chemical structures are illustrated below.



Lutein



Zeaxanthin

Owing to its three chiral centers, there are 2^3 or 8 stereoisomers of lutein. The principal natural stereoisomer of lutein is (3R,3′R,6′R)-lutein. Lutein is also known as xanthophyll (also, the group name of the oxygen-containing carotenoids), vegetable lutein, vegetable luteol and beta, epsilon-carotene-3,3′diol. The molecular formula of lutein is $C_{40}H_{56}O_2$ and its molecular weight is 568.88 daltons. The chemical name of the principal natural stereoisomer of lutein is (3R,3′R,6′R)-beta,epsilon-carotene-3,3′-diol.

Zeaxanthin has two chiral centers and therefore, 2^2 or 4 stereoisomeric forms. One chiral center is the number 3 atom in the left end ring, while the other chiral center is the number 3′ carbon in the right end ring. One stereoisomer is (3R,3′R)-zeaxanthin; another is (3S-3′S)-zeaxanthin. The third stereoisomer is (3R,3′S)-zeaxanthin, and the fourth, (3S,3′R)-zeaxanthin. However, since zeaxanthin, in contrast to lutein, is a symmetric molecule, the (3R,3′S)-and (3S,3′R)-stereoisomers are identical. Therefore, zeaxanthin has only three stereoisomeric forms. The (3R,3′S)-or (3S,3′R)-stereoisomer is called *meso*-zeaxanthin.

The principal natural form of zeaxanthin is (3R,3′R)-zeaxanthin. (3R,3′R)-and *meso*-zeaxanthin are found in the macula of the retina, with much smaller amounts of the (3S,3′S)-stereoisomer. It is thought that *meso*-zeaxanthin in the macula is formed from (3R,3′R,6′R)-lutein. Zeaxanthin is also known as beta, beta-carotene-3,3′-diol, *all-trans*-beta-carotene-3,3′-diol, (3R,3′R)-dihydroxy-beta-carotene (the principal natural stereoisomer), zeaxanthol and anchovyxanthin. Its molecular formula is $C_{40}H_{56}O_2$ and its molecular weight is 568.88 daltons. Zeaxanthin is the principal pigment of yellow corn *zea mays* L, from which its name is derived. It is also produced by certain bacteria, such as *Flavobacterium multivorum*, which are yellow in color.

Chicken egg yolks are a rich food source of lutein and zeaxanthin. The average amount of lutein in chicken egg yolk is approximately 290 micrograms per yolk, and the average amount of zeaxanthin, approximately 210 micrograms per yolk. Lutein-containing plant extracts, which are mainly derived from marigolds, are widely fed to chickens in order to give their egg yolks and skin a deeper yellow color. However, the downside of obtaining lutein and zeaxanthin via consuming egg yolks, is a possible elevation of LDL-cholesterol.

ACTIONS AND PHARMACOLOGY

ACTIONS

Lutein and zeaxanthin may be ophthalmoprotective.

MECHANISM OF ACTION

Lutein and zeaxanthin, which are naturally present in the macula of the human retina, filter out potentially phototoxic blue light and near-ultraviolet radiation from the macula. The protective effect is due in part, to the reactive oxygen species quenching ability of these carotenoids. Further, lutein and zeaxanthin are more stable to decomposition by pro-oxidants than are other carotenoids such as beta-carotene and lycopene. Zeaxanthin is the predominant pigment in the fovea, the region at the center of the macula. The quantity of zeaxanthin gradually decreases and the quantity of lutein increases in the region surrounding the fovea, and lutein is the predominant pigment at the outermost periphery of the macula. Zeaxanthin, which is fully conjugated (lutein is not), may offer somewhat better protection than lutein against phototoxic damage caused by blue and near-ultraviolet light radiation.

Lutein and Zeaxanthin, which are the only two carotenoids that have been identified in the human lens, may be protective against age-related increases in lens density and cataract formation. Again, the possible protection afforded by these carotenoids may be accounted for, in part, by their reactive oxygen species scavenging abilities.

PHARMACOKINETICS

Lutein and zeaxanthin exist in several forms. Nutritional supplement forms are comprised of these carotenoids either in their free (non-esterified) forms or in the form of fatty acid esters. Lutein and zeaxanthin exist in a matrix in foods. In the case of the chicken egg yolk, the matrix is comprised of lipids (cholesterol, phospholipid, triglycerides). The carotenoids are dispersed in the matrix along with fat-soluble

nutrients, including vitamins A, D and E. In the case of plants, lutein and zeaxanthin are associated with chloroplasts or chromoplasts.

The efficiency of absorption of lutein and zeaxanthin is variable, but overall appears to be greater than that of beta-carotene. Esterified forms of these carotenoids may be more efficiently absorbed when administered with high-fat meals (about 36 grams), than with low-fat meals (about 3 grams). Lutein and zeaxanthin esters are hydrolyzed in the small intestine via esterases and lipases. Lutein and zeaxanthin that are derived from supplements or released from the matrices of foods, are either solubilized in the lipid core of micelles (formed from bile salts and dietary lipids) in the lumen of the small intestine, or form clathrate complexes with conjugated bile salts. Micelles and possibly clathrate complexes deliver lutein and zeaxanthin to the enterocytes.

Lutein and zeaxanthin are released from the enterocytes into the lymphatics in the form of chylomicrons. They are transported by the lymphatics to the general circulation via the thoracic duct. In the circulation, lipoprotein lipase hydrolyzes much of the triglycerides in the chylomicrons, resulting in the formation of chylomicron remnants. Chylomicron remnants retain apolipoproteins E and B48 on their surfaces and are mainly taken up by the hepatocytes and to a smaller degree by other tissues. Within hepatocytes, lutein and zeaxanthin are incorporated into lipoproteins. Lutein and zeaxanthin appear to be released into the blood mainly in the form of high-density lipoproteins (HDL) and, to a lesser extent, in the form of very-low density lipoprotein (VLDL). Lutein and zeaxanthin are transported in the plasma predominantly in the form of HDL.

Lutein and zeaxanthin are mainly accumulated in the macula of the retina, where they bind to the retinal protein tuberlin. Zeaxanthin is specifically concentrated in the macula, especially in the fovea. Lutein is distributed throughout the retina.

The form of lutein in the plasma is (3R,3′R,6′R)-lutein. Zeaxanthin found in plasma is predominantly (3R,3′R)-zeaxanthin. Lutein appears to undergo some metabolism in the retina to *meso*-zeaxanthin.

INDICATIONS AND USAGE

Lutein and zeaxanthin show some promise of protecting against macular degeneration and may reduce the risk of cataracts in some.

RESEARCH SUMMARY

Epidemiological data have found a relationship between low plasma concentrations of the carotenoids, lutein and zeaxanthin, and risk of developing age-related macular degeneration (AMD). Laboratory evidence has suggested that supplemental lutein and/or zeaxanthin might help protect against AMD.

In a multi-center study of 356 subjects aged 55 to 80 years, all diagnosed with advanced stage AMD, a high dietary intake of carotenoids was associated with a 43% lower risk for AMD compared with those consuming low quantities of these carotenoids. Lutein and zeaxanthin were most strongly associated with reduced AMD risk.

Lutein esters, equivalent to 30 milligrams of free lutein per day, given over a period of 140 days, significantly increased macular pigment density in two subjects. A low density of this pigment is believed to be a risk factor for AMD. Controlled clinical trials are needed.

There is also epidemiological evidence that increased lutein and zeaxanthin intake are associated with lower risk of cataract development. In one epidemiological study, those found to have the highest intake of lutein and zeaxanthin had a 22% decreased risk of cataract extraction compared with those who consumed the least amounts of these carotenoids. These findings are consistent with those of similar studies. Again, clinical studies are needed.

CONTRAINDICATIONS, PRECAUTIONS, ADVERSE REACTIONS

CONTRAINDICATIONS

Lutein and zeaxanthin are contraindicated in those hypersensitive to any component of lutein and zeaxanthin-containing products.

PRECAUTIONS

Pregnant women and nursing mothers should try to obtain lutein and zeaxanthin from the consumption of five or more servings daily of fruits and vegetables. Chicken egg yolk is also rich in lutein and zeaxanthin, and pregnant women and nursing mothers who do not have problems with elevated cholesterol levels, should try to include this item in their diets, as well.

Lutein and zeaxanthin supplements should not be used for the treatment of vitamin A deficiency, since these carotenoids are not converted to vitamin A.

ADVERSE REACTIONS

Adverse reactions involving lutein and zeaxanthin have not been reported.

INTERACTIONS

DRUGS

Cholestyramine: Concomitant intake of lutein/zeaxanthin and cholestyramine may decrease the absorption of these carotenoids.

Colestipol: Concomitant intake of lutein/zeaxanthin and colestipol may decrease the absorption of these carotenoids.

Mineral oil: Concomitant intake of mineral oil and lutein/zeaxanthin may reduce the absorption of these carotenoids.

Orlistat: Orlistat may decrease the absorption of lutein/zeaxanthin.

NUTRITIONAL SUPPLEMENTS

Beta-carotene: Concomitant intake of beta-carotene and lutein may decrease the absorption of these carotenoids.

Medium-chain triglycerides: Concomitant intake of medium-chain triglycerides and lutein/zeaxanthin may enhance the absorption of these carotenoids.

Pectin: Concomitant intake of pectin and lutein/zeaxanthin may decrease the absorption of these carotenoids.

FOODS

Oils: Some dietary oil, such as corn oil, may increase the absorption of lutein/zeaxanthin, especially the ester forms of these carotenoids.

Olestra: Concomitant intake of olestra and lutein/zeaxanthin may decrease the absorption of these carotenoids.

OVERDOSAGE

Overdosage of lutein and zeaxanthin have not been reported in the literature.

DOSAGE AND ADMINISTRATION

Lutein/zeaxanthin supplements are available in free (non-esterified) and esterified (with fatty acids) forms, and as single ingredient or combination products. The amount of zeaxanthin in these products is considerably lower than that of zeaxanthin. Products that deliver higher amounts of zeaxanthin are being developed. Dosage is variable, and optimal dosage for ophthalmological health is not known. Dietary intake of lutein of 6.9-11.7 milligrams daily has been associated with a decreased risk of age-related macular degeneration. Nutritional supplements containing lutein deliver from 250 micrograms (0.25 milligrams) to 20 milligrams daily.

Green leafy vegetables are good dietary sources of lutein, but poor sources of zeaxanthin. Good dietary sources of zeaxanthin, include yellow corn, orange pepper, orange juice, honeydew, mango and chicken egg yolk.

LITERATURE

Berendschot TT, Goldbohm RA, Klö pping WA, et al. Influence of lutein supplementation on macular pigment, assessed with two objective techniques. *Invest Opthalmol Vis Sci.* 2000; 41:3322-3326.

Bone RA, Landrum JT, Dixon Z, et al. Lutein and zeaxanthin in the eyes, serum and diet of human subjects. *Exp Eye Res.* 2000; 71:239-245.

Bone RA, Landrum JT, Friedes LM, et al. Distribution of lutein and zeaxanthin stereoisomers in the human retinal. *Exp Eye Res.* 1997; 64:211-218.

Bone RA, Landrum JT, Tarsis SL. Preliminary identification of the human macular pigment. *Vision Res.* 1985; 25:1531-1535.

Bowen PE, Clark JP. *Lutein esters having high bioavailability.* International patent publication number: WO 98/45241. International publication date: 15 October 1998.

Brown L, Rimm EB, Seddon JM, et al. A prospective study of carotenoid intake and risk of cataract extraction in U.S. men. *Am J Clin Nutr.* 1999; 70:517-524.

Chasan-Taber L, Willett WC, Seddon JM, et al. A prospective study of carotenoid and vitamin A intakes and risk of cataract extraction in U.S. women. *Am J Clin Nutr.* 1999; 70:509-516.

Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids. Washington, DC: National Academy Press; 2000:325-382.

Erdman JW Jr. Variable bioavailability of carotenoids from vegetables (editorial). *Am J Clin Nutr.* 1999; 70:179-180.

Garnett KM, Glerhart DL, Guerra-Santos LH. *Method of making pure 3R-3' R stereoisomer of zeaxanthin for human ingestion.* United States Patent Number: 5,854,015. Date of Patent: Dec. 29, 1998.

Hammond BR Jr, Wooten BR, Snodderly DM. Density of the human crystalline lens is related to the macular pigment carotenoids, lutein and zeaxanthin. *Optom Vis Sci.* 1997; 74:499-504.

Handelman GJ, Nightingale ZD, Lichtenstein AH, et al. Lutein and zeaxanthin concentrations in plasma after dietary supplementation with egg yolk. *Am J Clin Nutr.* 1999; 70:247-251.

Khachik F. *Process for extraction and purification of lutein, zeaxanthin and rare carotenoids from marigold flowers and plants.* International patent publication number: WO 99/20587. International publication date: 29 April 1999.

Koonsvitsky BP, Berry DA, Jones MB, et al. Olestra affects serum concentrations of alpha-tocopherol and carotenoids but not vitamin D or vitamin K status in free-living subjects. *J Nutr.* 1997; 127(8 Suppl):1636S-1645S.

Kostic D, White WS, Olson JA. Intestinal absorption, serum clearance, and interactions between lutein and beta-carotene when administered to human adults in separate or combined oral doses. *Am J Clin Nutr.* 1995; 62:604-610.

Landrum JT, Bone RA, Joa H, et al. A one year study of the macular pigment: the effect of 140 days of a lutein supplement. *Exp Eye Res.* 1997; 65:57-62.

Mares-Perlman JA. Too soon for lutein supplements (editorial). *Am J Clin Nutr.* 1999; 70:431-432.

Nussbaum JJ, Pruett RC, Delori FC. Historic perspectives. Macular yellow pigment. The first 200 years. *Retina.* 1981; 1:296-310.

Olson JA. Carotenoids. In: Shils ME, Olson JA, Shike M, Ross AC. *Modern Nutrition in Health and Disease*. Baltimore, MD: Williams and Wilkins; 1999:525-541.

Roodenburg AJ, Leenen R, van het Hof KH, et al. Amount of fat in the diet affects bioavailability of lutein esters but not of alpha-carotene, beta-carotene, and vitamin E in humans. *Am J Clin Nutr*. 2000; 71:1187-1193.

Siems WG, Sommerburg O, van Kuijk FJ. Lycopene and beta-carotene decompose more rapidly than lutein and zeaxanthin upon exposure to various pro-oxidants in vitro. *Biofactors*. 1999; 10:105-113.

Sommerburg O, Keunen JE, Bird AC, et al. Fruits and vegetables that are sources for lutein and zeaxanthin: the macular pigment in human eyes. *B J Opthalmol*. 1998; 82:907-910.

Sommerburg OG, Siems WG, Hurst JS, et al. Lutein and zeaxanthin are associated with photoreceptors in the human retina. *Curr Eye Res*. 1999; 19:491-495.

van den Berg H. Effect of lutein on beta-carotene absorption and cleavage. *Int J Vitam Nutr Res*. 1998; 68:360-365.

van het Hof KH, Brouwer IA, West CE, et al. Bioavailability of lutein from vegetables is 5 times higher than that of beta-carotene. *Am J Clin Nutr*. 1999; 70:261-268.

Luteolin

DESCRIPTION

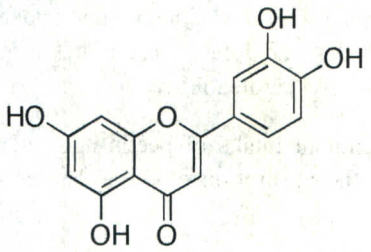
Luteolin is a polyphenolic substance and a member of the flavone subclass of flavonoids.

Conjugated forms of luteolin, including luteolin-7-glucoside, luteolin 7-O-beta-glucuronide and luteolin 7 O-[beta-glucuronosyl-(1>2)-beta-glucuronide] are found naturally in many plants, including celery (*Apium graveolens*), green peppers (*Capsicum annuum*), perilla leaf and seed (*Perilla frutescens*), dandelion (*Taraxacum officinale*), balsamic sage (*Salvia tomentosa*), thyme (*Thymus vulgaris*), chamomile tea (*Matricaria recutita*) and Japanese honeysuckle (*Lonicera japonica*).

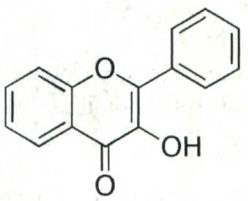
Luteolin is chemically described as 2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-4*H*-chromen-4-one. It is also known as 3′,4′,5,7-tetrahydroxyflavone, 2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-4*H*-1-benzopyran-4-one, digitoflavone, daphnetflavonol and flacitran. Its CAS registry number is 491-70-3, its empirical formula is $C_{15}H_{10}O_6$ and its molecular weight is 286.24.

Luteololin is of interest for its possible anti-inflammatory, anticancer and antiatherogenic activities. Recently, it has been found that luteolin may even help to ameliorate the niacin-induced flush.

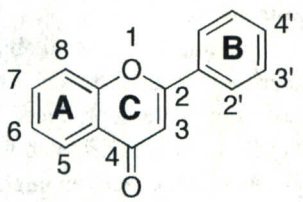
All flavonoids possess a basic 15-carbon skeleton that can be represented as C_6-C_3-C_6. The common structure is that of a diphenylpropane molecule, consisting of two aromatic rings linked through the three carbons. Flavones possess a carbonyl group on position 4 of the C ring. Luteolin (tetrahydroxyflavone) possesses hydroxyl groups on positions 3′ and 4′ of the B ring and 5 and 7 of the A ring. The chemical structures below are described within this monograph.



Luteolin



Flavonol Skeleton



Flavonoid Skeleton

ACTIONS AND PHARMACOLOGY

ACTIONS

Luteolin has antioxidant activity and possible activity against the niacin (nicotinic acid)-induced flush. Luteolin may also have antiatherogenic, anticancer, anti-inflammatory, antileishmanial and otoprotective activities.

MECHANISM OF ACTION

Activity against the niacin (nicotinic acid)-induced flush: Niacin or nicotinic acid is one of the two forms of vitamin B_3 (See Niacin). At high doses, niacin is an effective lipid-modifying agent, lowering LDL cholesterol, raising HDL cholesterol and lowering triglyceride levels. The problem is that most people cannot tolerate the major adverse event of niacin, the so-called niacin flush, leading to its discontinuation. The niacin-induced flush is thought to involve the release of prostaglandin D_2 (PGD_2) from the skin. Pharmaceutical companies are researching possible PGD_2 and