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LUTEIN – THE LESS EXPLORED CAROTENOID

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ABSTRACT

Lutein and zeaxanthin are xanthophyll carotenoids found particularly in dark-green leafy vegetables and in egg yolks. They are widely distributed in tissues and are the principal carotenoids in the eye lens and macular region of the retina. Epidemiologic studies depicts an inverse relationship between xanthophyll intake and Retinitis Pigmentosa (RP), cataract and Age-Related Macular Degeneration (ARMD) thus suggesting a protective role of these compounds in the eye. Some observational studies have also shown these xanthophylls may help reduce the risk of certain types of cancer and diabetes. It is also known to have beneficial effects on skin health. Emerging studies suggest as well a potential contribution of lutein and zeaxanthin to the prevention of various cardiovascular diseases too. The use of lutein as a nutritional supplement has been explored in recent years. It is used as a major pharmaceutical but its application as a nutraceutical still needs to be emphasised upon as its industrial application will be very promising in near future. Lutein is a promising biologically active component in the food industry.

KEYWORDS: *Lutein, Zeaxanthin, Xanthophyll, Nutraceutical, ARMD, Cancer.*

INTRODUCTION

Carotenoids are a family of pigmented compounds that are synthesized by plants and microorganisms but not animals. In plants, they contribute to the photosynthetic machinery and protect them against photo-damage. Fruits and vegetables constitute the major sources of carotenoid in human diet.[1] They are present as micro-components in fruits and vegetables and are responsible for their yellow, orange and red colours. In recent years the antioxidant properties of carotenoids has been the major focus of research. More than 600 carotenoids have so far been identified in nature. However, only about 40 are present in a typical human diet. Of these 40 about 20 carotenoids have been identified in human blood and tissues. Close to 90% of the carotenoids in the diet and human body is represented by carotene, lycopene, lutein and cryptoxanthin.[2] Lutein is a member of Xanthophyll family which mostly found in green leafy vegetables like pea, broccoli, corn, spinach, carrot, egg yolk etc. and flowers like marigold.[3]

Lutein is the active carotenoid and is potent, natural source antioxidant. It is one of the most widely distributed carotenoids in fruits and vegetables frequently consumed in daily diet by different populations. It is naturally derived from marigold flowers and contains a normal blend of carotenoids including zeaxanthin and cryptoxanthin. Xanthophyll is primarily been used as a natural colorant due to its orange-red color. Lutein absorbs blue light and therefore appears yellow at low concentrations and orange-red at high concentrations. On an average it accounts for approximately 48% of the total xanthophylls in green leafy vegetables.[4] Lutein is also known to act as an important dietary nutrient for prevention against eye diseases like cataract and age-related macular degeneration.[5] Lutein is also known to have positive health effects for people suffering from cardio vascular diseases.[6] Carotenoid mixtures including synergistic effects of lutein with lycopene is found to have preventive effects against oxidative damage.[7]

The use of lutein as a nutritional supplement has been widely explored in recent years. It is used as a major pharmaceutical but its application as a nutraceutical still needs to be emphasised upon as its industrial application will be very promising in near future. Lutein is a promising biologically active component in the food industry.

Structure and chemistry of lutein

The structure of lutein can be described as a long carbon chain with alternating single and double carbon-carbon bonds with attached with the methyl side groups. The carbon backbone has two ends and both have a molecule that contains a cyclic hexenyl structure with an attached hydroxyl group. (Fig.1) Structurally, with nine double bonds it is responsible for the absorbance of certain wavelengths of light and the emission of other wavelengths leading to the characteristic colour properties of these molecules. As lutein can absorb blue light, so it has a yellow or orange like appearance depending on its concentration. The main isomer of lutein presents in plants and vegetables is its Trans form, but during processing it results in significant isomer changes.[8] The chemical formula of lutein is $C_{40}H_{56}O_2$ and the molecular weight is 568.88.

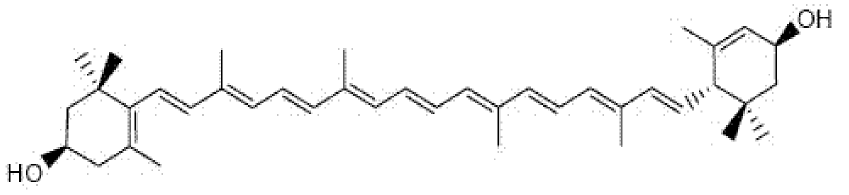

Fig.1 Planer structure of Lutein

Sources of lutein

Human cannot synthesize lutein and uptake is therefore dependent on the consumption of diet including certain fruits, leafy green vegetables and egg yolks.[9] Lutein occurs as a natural pigment in commonly found in fruits and green vegetables like maize, alfalfa, peas, drumstick, spinach, broccoli, lettuce, coriander, cucumber, kiwi, orange pepper, pumpkin, egg yolk, pistachio etc**.** Other sources of lutein in fruits and vegetables are highlighted in Table 1.[10]

These food sources receive all of their yellow-to-orange color from their zeaxanthin and lutein content. In contrast, green leafy plant foods typically contain high levels of lutein, but very little zeaxanthin. This difference is due to the fact that green leaves form zeaxanthin under full sunlight and remove zeaxanthin when no longer exposed to full sunlight. In a study conducted in Boston, it was found that corn and corn products were major sources of dietary zeaxanthin, while green leafy vegetables were major sources of dietary lutein.[11]

Flower like marigold petals contain high amount of lutein and one of the richest source of lutein. *Bombyxmori*, yellow cocoons of silkworms, have found to contain approximately 88% of the xanthophyll lutein.[12] The silk lutein extract from yellow cocoons could alternatively become a valuable dietary resource and may expand uses of lutein in the field of medicine. As humans cannot synthesize lutein therefore alternative sources of dietary lutein is continuously being identified and studied upon.

Table 1 Comparison of the lutein and zeaxanthin concentrations in selected foods

Food item	Lutein and zeaxanthin (µg/100g)	Serve size (grams) which provides 100 µg lutein and zeaxanthin	Approximate estimate of household measure which provides 100 µg lutein and zeaxanthin[1]
Spinach	11,308	0.9	¼ teaspoon
Green Peas	2,400	4	1 teaspoon or 3 peas
Broccoli	1,403	7	1 tablespoon

Food item	Lutein and zeaxanthin (µg/100g)	Serve size (grams) which provides 100 µg lutein and zeaxanthin	Approximate estimate of household measure which provides 100 µg lutein and zeaxanthin[1]
Corn	949	11	2 teaspoons
Carrots	687	14	1 tablespoon of slices
Beans	564	18	1 ½ tablespoons
Egg, cooked	354	28	½ large egg or1/5 cup chopped egg
Oranges	129	78	¾ of one small orange or 2/5 cup of orange sections
Tomatoes	123	81	3 thick slices or ½ cup of cut tomatoes
Orange juice	115	87	1/3 cup
Peaches	91	110	¾ cup slices
Bread	48	208	6-7 slices
Pears	34	294	1 and 1/5 cup of pear halves
Cucumber	23	435	4 and 1/5 cup of slices

Source: United States Department of Agriculture 2008.

[1] One level metric cup = 250 mL. One level metric tablespoon = 20 mL. One level metric teaspoon = 5 mL.

Microalgae as the source of lutein

Compared with higher plants, another main source of naturally occurring carotenoids, algae can be cultivated in bioreactors so that a continuous and reliable source can be guaranteed.[13] Besides, the growth of algae in photobioreactors is independent of season or weather, so that a homogeneous biomass which is ready for processing without the labor-intensive separation can be obtained. Lutein belong to primary carotenoids. They are located within the thylakoidal membrane to quench free radicals in chlorophylls. Distribution of lutein in some representative algae is summarized in Table 2.[14]

Table 2. Distribution of lutein in algae

	Microalgae	Quantity (mg g^{-1})
Lutein	*Chlorella protothecoides*	4.6
	Dunaliellasalina	6.6
	Scenedesmusalmeriensis	5.3
	Galdieriasulphuraria	0.4

Extraction and analysis of lutein

Lutein is a natural lipophilic carotenoid and is soluble in solvents and oils. Cell disruption, alkaline treatment and solvent extraction, saponification, chromatography and spectrophotometry are various techniques used for lutein extraction. Lutein was extracted from dried microalga biomass of the specie *Scenedesmus almeriensis*; cell disruption, alkaline treatment and solvent extraction resulted in extraction of 99% of the total lutein content present in the biomass. This technique is widely accepted in industries as it results in efficient recovery of lutein from microlaga biomass.[15] Crude lutein was also extracted from the microalga *Chlorella vulgaris* using dichloromethane followed by saponification, 85-91% of lutein was recovered with a final purity upto 98%.[16] Non phenolic content of residual green tea (*Camellia sinensis*) was used to extract significant amount of lutein after hot water extraction using the aluminum chloride method and using silica gel TLC plate.[17] Similar results were found when green tea was subjected to solvent extraction and ultra-performance liquid chromatography (UPLC) system with a recovery of approximately 93.73%. This study also revealed that the green tea by-products, which are discarded after producing green tea beverages, might be used as a great resource for massive lutein production.[18] Lutein was also extracted from spinach using the same techniques resulting in an approximate yield of 90%.[19]

Storage and stability of lutein

Low bio accessibility and stability of carotenoids is a challenge for their application as functional foods and in pharmaceutical and nutraceutical industries.[20] The stability of lutein in sunflower and rice bran oils was investigated in the temperature range 25–40°C. Experiments were made using a standardized plant extract at 5% by weight of lutein derived from the flowers of *Tageteserecta L*. Samples of the pigment in oil were incubated at each temperature for up to 10 days and the time course of degradation was monitored. A kinetic analysis of the data showed that thermal degradation follows first-order kinetics, with apparent activation energies of 60.9 kJ mol −1 (in sunflower oil) and 44.9 kJ mol −1 (in rice bran oil). From the estimated kinetic parameters, the carotenoid half-life at 4 and 20 °C were determined. The results obtained indicate that lutein is more stable in sunflower oil. The observed differences in stability could be a reflection of the different fatty acid composition of the two oils and the presence of endogenous antioxidants.[21]

The content and stability (retention) to Dry Heat in a Conventional Oven (DHCO) and extrusion of carotenoids including lutein in sorghum genotypes were evaluated. The content and stability was found to be decreases using DHCO and extraction techniques.[22] Lutein was incorporated into liposomes and it was demonstrated that a liposomal membrane can strongly retain lutein, thereby improving the storage stability.[23] Lutein and zeaxanthin enriched health food (ready mix) was developed and studied at different temperature and storage conditions. Results revealed a decrease in the L+Z level (4.70, 9.24, and 13.85%) of ready-mix stored at 4, 27 and 37°C, respectively. Critical relative humidity and critical moisture content of the product was 64% and 12.24%, respectively. The effect of light on a beverage containing lutein, whey and limonene was investigated using photochemical reactor at different wavelengths. Lutein degradation occurred at UV (200-400 nm) and 463 nm wavelengths.[24] Similar study was conducted on the thermal treatment and light exposure on degradation and isomerization of lutein.[25] Lutein stability has also been studied during baking and storage conditions. Lutein and its isomers were separated and extracted with water-saturated 1-butanol, it was concluded that baking led to significant decrease in all-trans-lutein and consecutive storage at ambient temperature had a slight impact on the content of all-trans-lutein.[26]

Continuous exposure of lutein-containing samples to cold white fluorescent light (4600 lux) at 25°C resulted in the degradation of lutein at 0.8%-10.7% per day in the samples containing ascorbic acid, ascorbic acid + KOH and H_2O (as control) over a period of 75 days. It was found that ascorbic acid could retard lutein degradation (0.04% - 2.5% per day) at temperatures from −30°C to 50°C under the alkaline condition in darkness.[27]

A study with the objective of monitoring the effects of gamma irradiation and storage on the content of lutein and zeaxanthin in egg yolk samples was conducted. Liquid, frozen and dried egg samples were subjected to gamma irradiation doses of 0, 1, 2 and 3 kGy followed by storage of liquid samples at -4 ± 1 C for 21 days, frozen samples at -18 ± 1 C and dried samples at room temperature for 1 year. It was observed that concentrations of both lutein and zeaxanthin were decreased significantly (P\0.05) after irradiation and during storage. The mechanism for radiation-induced degradation was proposed as radical formation which initiate chain reactions. It was suggested that during storage active radical species and oxygen caused the degradation.[28]

Biochemistry of Lutein

Lutein is an oxycarotenoid, or xanthophyll, containing 2 cyclic end groups (one beta - ionone ring and one alpha - ionone ring) and the basic C40 isoprenoid structure which is common to all carotenoids. Although the polyene chain double bonds present in lutein could exist in a *cis* or *trans*conformation, synthesize large number of possible mono-*cis* and poly-*cis* isomers, the vast majority of carotenoids are in the all-trans configurations.[29]

The two rings have been hydroxylated at the 3 and 3' positions, they are called beta (β, double bond between C5=C6) and epsilon (ε, double bond between C4=C5). The location of a single double bond is the only difference between lutein and zeaxanthin (visual comparison). Lutein has one β-ring and one ε-ring, zeaxanthin has two β-ring. Chemically lutein and zeaxanthin are isomers, although not stereoisomers and occur naturally as all-trans (all-E - note in carotenoids trans is synomous with E unless there are oxygens substitutions on the carotenoid chain) geometric isomers.[30]

Lutein has three chiral-carbons which are enantiomeric (optically active). These centers are shown in the above image located at C3, C3' and C6' and are designated as S (sinister as compared to R, rectus). Stereo chemical centres can lead to important information on the stereo specificity of catalytic events. With carotenoids however the number of stereoisomers is an advantage. Oxidized carotenoid rings show a high degree of tautomerization (a form of keto-enol isomerization) and a substrate or product can often times be represented by several tautomeric isomers. In many cases tautomeric isomers of carotenoids have low energy barriers separating them from R and S configurations. As a result, often times these stereocenters are lost in the shuffle so far as an initial reference point may be defined. Fortunately, the high degree of conjugation in carotenoids tends to favor those tautomers which are in resonance with the backbone of the carotenoid. Several sterol enzymes have been found to assist in keto-enol tautomerization (enzyme assisted isomerisation) favoring one isomer over another.[31]

Bioavailability of lutein

Xanthophylls are fat-soluble nutrients, bioavailability to tissues is dependent on a number of factors, including nutrient source (whole food or supplement), state of the food (raw, cooked, or processed), extent of disruption of the cellular matrix via mastication and digestive enzymes and absorption by the enterocytes of the intestinal mucosa (primarily the duodenum). Cooking of lutein/zeaxanthin-containing foods may increase bioavailability by disrupting the cellular matrix and the carotenoid-protein complexes.[32]

Fats and oils increase the bioavailability of lipophilic molecules like lutein.[33] Dietary olive oil rich containing oleic acid and wheat germ oil has proven to increase the bioavailability and accumulation of lutein in lutein-deficient mice by modifying the intestinal triacylglycerol lipase activity.[34] Saturated Fatty Acids also rendered a higher bioavailability of lutein and zeaxanthin, as compared with fats rich in MUFA and PUFA.[35]

Micro emulsification nanotechnology has shown to increase the bioavailability of lutein, when tested on egg yolks.[36]

The effects of thermal processing on the bioavailability of lutein and zeaxanthin had also been studied, the results were dependant mainly on the severity of the thermal treatments applied. At lower temperature ranges (60–100°C), which are used for blanching, pasteurisation and drying, plant tissues are disrupted and cell walls and membranes are destroyed, leading to an increase in carotenoid extraction and retention, whereas isomerisation is negligible. Higher temperatures (>100°C), practiced for canning and sterilisation, cause major *cis*-isomerisation favouring carotenoid uptake. Carotenoids found in canned or sterilised products tend to have a high storage stability. In contrast, carotenoids in fresh produce and frozen and dry products are very susceptible to oxidative deterioration, especially during production and storage of convenience products (eg, pizza).[37]

Absorption of lutein

Lutein as all carotenoids is more readily absorbed into the body if provided a lipid and are transported by the lymphatic system into the liver. Thus a high cholesterol or lipid diet may enhance the absorption of carotenoids and vice versa. Dietary olive oil rich in oleic acid improves the bioavailability and absorption kinetics of lutein in lutein-deficient mice by modifying the intestinal triacylglycerol lipase activity.[38] Lutein bioavailability was also seen to be improved if given with doses of wheat germ oil.[39]

Certain drugs, nutritional supplements and foods have been reported to decrease the absorption of lutein/zeaxanthin. Cholesterol-lowering medications, including cholestyramine (Questran®) and colestipol (Colestid®) and Xenocal®, a drug used to treat obesity, may reduce the absorption of fat-soluble carotenoids.[40] Proton-pump inhibitors such as Prilosec ®, Losec®, Prevacid®, Aciphex®, Protonix® and Pantoloc® increase gastric pH and have been shown to decrease the absorption of a single dose of betacarotene. Whether or not these drugs have the same effect on lutein/zeaxanthin absorption has not been determined. Mineral oil, corn oil, medium chain triglycerides, olestra and pectin may also inhibit the absorption of lutein and zeaxanthin.[41]

The concentrations of various carotenoids in human serum and tissues are highly variable and depend on food sources, efficiency of absorption, and amount of fat in the diet. Lutein is transported by high density lipoprotein (HDL) and, to lesser extent by very low density lipoprotein. The serum concentration of carotenoids after single dose peaks at 24 to 48 hours post dose. The average lutein concentration in human serum is 280nM.[42] Lutein is primarily stored in adipose and liver. Of all the carotenoids circulating in the body, only two polar species, lutein and zeaxanthin, are contained in the macula. It is assumed that lutein is excreted through the bile and kidneys.[43]

Recommended dosage of lutein

Average daily intake for lutein and zeaxanthin (in the form of capsules) in the United States is 2.0-2.3 mg daily for men and 1.7-2.0 mg daily for women although dietary intakes of approximately 6-20 mg lutein daily appear to be necessary to decrease risk of macular degeneration. If taken in supplement form, lutein and zeaxanthin are available in either the free or esterified forms, which appear to have comparable bioavailability.[44] Although commercially available lutein/zeaxanthin supplements often contain significantly more lutein than zeaxanthin, new products are being developed with higher amounts of zeaxanthin. Typically, lutein supplements are available in either 6- or 20- mg tablets or capsules. While the 6-mg dose is based on early studies, the 20-mg dose is more typical and is usually taken once daily.[45]

Toxicity/ side effects

No toxicities or adverse reactions have been reported in the scientific literature for lutein/zeaxanthin at doses of up to 40 mg daily for two months. Fijians consume an average of 25 mg lutein daily throughout a lifetime without any toxic effects. High doses of beta-carotene supplements (>30 mg daily) have been associated with carotenodermia and the same may occur with high doses of lutein and zeaxanthin. Studies of lutein and zeaxanthin in pregnant and nursing women have not been conducted, so pregnant and nursing women should obtain lutein/ zeaxanthin from daily servings of fruits, vegetables and egg yolks. Ames test[46] has demonstrated an absence of any mutagenic effect for purified lutein. It is lipid soluble and has shown positive effects in various studies conducted on infants as well as healthy subjects.[47]

Mechanism of action

Lutein and zeaxanthin are powerful antioxidants and lutein is widely known as the primary nutrient for protecting ocular function. It has long been thought that carotenoid intake also reduces the risk of certain forms of cardiovascular disease[48] stroke and cancer.[49]

After lutein and zeaxanthin are absorbed by the enterocytes they are transported across the intestinal lumen and incorporated into the chylomicrons. They reach the circulating blood and are subsequently taken up by hepatocytes, entering the hepatic circulation where they are incorporated into lipoproteins. In humans, low- and high-density lipoproteins transport lutein and zeaxanthin via the systemic circulation to various tissues.[50] Data on xanthophyll absorption is limited, but studies involving single dietary doses indicate lutein reaches peak concentrations in the chylomicron fraction at approximately two hours post-ingestion and peaks in serum at about 16 hours post-ingestion.[51] Lutein absorption from a purified crystalline lutein supplement is almost twice that from spinach or other vegetable sources. Non-dietary factors affecting absorption and bioavailability of lutein and zeaxanthin include age, body composition, gender, malabsorption of fats, alcohol consumption, smoking and liver or kidney disease.[52]

Interaction of lutein with other nutrients

Although inconclusive, some studies have demonstrated a competitive inhibition for absorptionamong carotenoids. The two carotenoids most often examined have been beta-carotene and lutein. Competition for absorption seemed only to be a factor in short-term studies (less than two years), while longer studies has not demonstrated this effect. For example, β- carotene was reported to decrease lutein absorption, while lutein both decreased and increased β-carotene absorption in different subjects.[53] In another study, lutein impaired β-carotene absorption, but did not affect the secretion of retinyl esters in chylomicrons. The interaction between β-carotene and lutein appeared to be somewhat specific, since β-carotene absorption was not affected by lycopene. Possible sites for pre-absorptive interactions between carotenoids include competition for incorporation into micelles, cellular uptake from the micelle, binding to BCO1 and incorporation into chylomicrons.[54]

Lutein and health benefits

Lutein as an Antioxidant

Lutein possesses pronounced free radical scavenging ability due to its polarity and number of conjugated double bonds (Fig 1). Lutein significantly enhances the antioxidant enzyme system in blood and liver tissue. These results indicate that free lutein has a profound effect on the antioxidant defence system. The antioxidant activity of lutein may be attributed to its unique chemical structure. Lutein not only has conjugated double bonds but also has two hydroxyl groups on both ends making it stronger antioxidant as compared to other carotenoids. Carotenoid lutein may reduce the oxidative damage or minimize the damage due to oxidative stress, by limiting the degree to which oxygen penetrates membranes.[55]

Age Related Macular Degeneration (ARMD)

Age-related macular degeneration is an eye disease in which the macula, the central part of the retina, deteriorates and dies, causing central vision loss and making driving and reading impossible. The "dry" form of the disease typically develops after cellular debris collects under the macula. In the "wet" type, abnormal blood vessels form and leak under the retina, which causes a scar to form and destroys central vision. There is no cure and current treatments are largely ineffective.[56]

For people over age 75, about 30 percent—10 million—are affected by the disease to some extent. Of those, 2 million have severe vision loss in at least one eye, which happens at the end stage. The disease is becoming more prevalent as the population ages.[57]

Only two carotenoids, namely lutein and zeaxanthin are selectively accumulated in the human eye retina from blood plasma where more than twenty other carotenoids are available.[58] The lens and retina of the human eye are exposed constantly to light and oxygen. In situ photo transduction and oxidative phosphorylation within photoreceptors produces a high level of phototoxic and oxidative related stress, lutein and zeaxanthin protects the Retinal Pigment Epithelium (RPE) from this stress.[59]

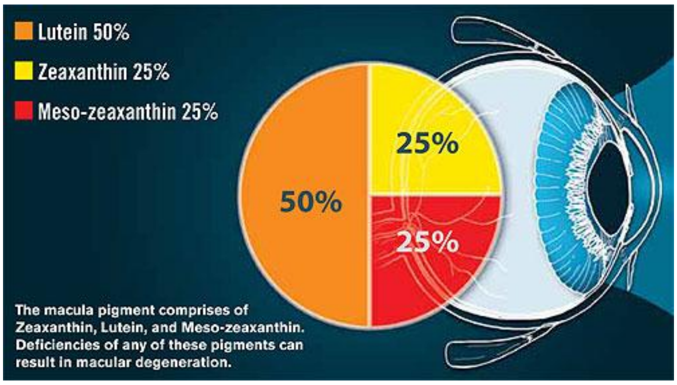

Fig2. Composition of lutein and zeaxanthin in macula of the eye

Many epidemiological studies suggest that the higher consumption of lutein and zeaxanthin is associated with lower risk of AMD.[60] The ability of these xanthophylls to filter out blue light (all carotenoids absorb blue/green light) and to quench singlet oxygen (in organic solution the quenching rate constant depends on the number of conjugated double bonds) is not better than that of other plasma carotenoids.[61] A daily intake of lutein and zeaxanthin in diet have shown to decrease the incidences of ARMD in experimental groups.[62] In a randomized, double blind, placebo control trial lutein and zeaxanthin supplementation in the subjects lead to increase in macular pigment optical density, thus increasing retinal sensitivity in patients suffering from ARMD.[63] Another study conducted in Europe with the aim to evaluate ophthalmologists' opinion of and use of, micro nutritional dietary supplements proved that maximum ophthalmologists consider lutein, zeaxanthin, zinc, omega-3 and vitamins to be the most important components of nutritional supplements for approximately 65% of the total patients suffering from ARMD.[64]

A study conducted on 70 old age people suffering from ARMD, supplemented with 10mg daily dose of lutein for 12 months, showed the significant effects of lutein on the management of ARMD.[65] Intervention studies for ARMD subjects supplemented with lutein-zeaxanthin combinations have proven beneficial with 40% reduced risk.[66] In a hospital based study higher dietary intake of carotenoids, especially lutein-zeaxanthin, was associated with lower risk for ARMD.[67]

LUTEGA study, double-blind, placebo-controlled clinical trial, with the objective of assessing long term effects of supplementation with lutein, zeaxanthin, omega-3-longchain-polyunsaturated-fatty-acids and antioxidants on macular pigment optical density (MPOD) in patients with non-exudative age-related macular degeneration (ARMD) was conducted on 172 ARMD subjects. Results revealed a protective effects on the macula in the ARMD patients.[68]

The large Lutein Antioxidant Supplementation Trial (LAST) was designed to determine the effects of supplementation on density of macular pigments in people with age-related macular degeneration. Subjects received 10 mg lutein alone; lutein with vitamins, minerals and antioxidants; or a placebo. The density of macular pigment increased in both supplemented groups, and declined significantly in the placebo recipients. Most vitally, this study established that people with the lowest pigment density (and therefore in greatest need of supplementation), obtained the greatest benefit from supplementation. The authors concluded that "If a deficiency in macular pigment optical density is accurately diagnosed, effective interventions should be able to re-establish this prophylactic barrier".[69]

Cataract

Cataracts are developmental or degenerative opacities of the lens that result in a gradual, painless loss of vision. Often it develops slowly. Symptoms may include faded colors, blurry vision, halos around light, trouble with bright lights, and trouble seeing at night. This may result in trouble driving, reading, or recognizing faces. Poor vision may also result in an increased risk of falling and depression. Cataracts are the cause of half of blindness and 33% of visual impairment worldwide.[70] Oxidative insult appears to be a precipitating factor in cataracts, resulting in the development of insoluble, oxidized lens proteins. Higher levels of hydrogen peroxide have been found in cataractous lenses compared to normal lenses, indicating oxidative stress.[71]

Studies examining lutein and zeaxanthin levels in extracted cataractous lenses have found up to three-fold higher levels in the newer epithelial tissue of the lens than in the older inner cortex portion. The epithelial cortex layer comprises 50 percent of the tissue, yet it has been found to contain 74 percent of the total lens lutein and zeaxanthin, supporting the hypothesis that these nutrients are protective against the oxidative damage causing cataract formation.[72]

The only randomized, double-blind trial on carotenoid supplementation and age-related cataracts measured visual acuity, glare sensitivity and serum carotenoid levels in 17 clinically diagnosed patients. Patients received 15 mg lutein three times weekly for two years and were compared to patients receiving 100 mg alpha-tocopherol or placebo for the same period. In patients receiving lutein, statistically significant improvements in visual acuity and glare sensitivity and increased serum concentrations of lutein were observed, compared to the alpha-tocopherol and control patients.[73]

The Nurses' Health Study examined the effect of 12 years of carotenoid consumption on the risk of cataract formation in 77,466 female nurses, ages 45 and over. After controlling for other risk factors, nurses in the highest quintile for lutein and zeaxanthin consumption had a 22-percent decreased risk for cataract extraction, compared with those in the lowest quintile.[74] Numerous other observational studies have found that increased consumption of foods high in lutein/zeaxanthin is associated with a decreased risk for cataracts or cataract extraction in both men and women.[75] These studies provide strong evidence for a protective role for lutein/zeaxanthin against development of cataracts.

Retinitis Pigmentosa

Retinitis pigmentosa (RP) is a rare, inherited, degenerative disease characterized by atrophy of the light-sensing rods in the retina. The rods are responsible for vision in low-light situations; therefore, early RP (often in childhood) is frequently characterized by poor night vision. A progressive loss of peripheral vision occurs over time, resulting in tunnel vision in late stages of the disease.[76]

The treatment for Retinitis Pigmentosa is limited, high-dose vitamin A supplementation has been shown to slow the degeneration.[77] In a study, it was found that 40 mg lutein daily for nine weeks significantly improved visual acuity among 16 RP patients. Testing of visual acuity was done via computer simulated self-test by RP patients. Ongoing double blind, placebo-controlled trials are examining the effects of lutein supplementation in patients with RP.[78]

Cardiovascular health

One of the main manifestations of vascular aging is the development of atherosclerotic lesions. These lesions become unstable and prone to rupture due to the formation of reactive oxygen species (ROS) that are produced by the inflammatory milieu in the atherosclerotic plaque.[79]

Lutein supplementation reduce biomarkers of CVD risk via decreased lipid peroxidation and inflammatory response by increasing plasma lutein concentrations and antioxidant capacity.[80] It was also documented in a study that higher serum levels of carotenoids (lutein) were associated with decreased risk of elevated serum N-terminal pro b-type natriuretic peptide (NT-pro BNP) levels, suggesting a role in preventing cardiac overload; moreover, high plasma levels of β-cryptoxanthin and lutein were associated with lower risk of acute myocardial infarction. Also, patients with coronary artery disease showed to have lower plasma levels of lutein, zeaxanthin, β-cryptoxanthin, α-carotene, β-carotene, and lycopene compared to healthy subjects.[81]

A study conducted on 123 patients suffering from myocardial infarction showed that the serum levels of carotenoids including lutein (P=0.09) was inversely associated with the condition.[82] A study performed on 44 men with no previous incidence of any cardiovascular disease showed an inverse correlation between lutein intake and risk for ischemic stroke when followed up for 8 years.[83] Lutein supplementation was also found to have an inverse relationship with development of carotid artery intima-media thickness in 144 Chinese subjects of age group 45-68 years. The supplementation led to increase in serum concentration of lutein, which showed positive results.[84] Supplementation with 10 or 20 mg/d of lutein has proven to be beneficial for cardiovascular diseases in subjects.[85]

Cancer prevention

Cancer, also known as a malignant tumor or malignant neoplasm, is a group of diseases involving abnormal cell growth with the potential to invade or spread to other parts of the body. Oxidative stress has been considered to play an important role in the pathogenesis of cancer.[86]

Antioxidant properties of carotenoids including lutein have major role in preventing cell carcinomas. Lutein is found to have anti-inflammatory and anti-tumor properties. Effect of lutein was studied in prostate cancer patients in combination with chemotherapeutic agents. The results highlighted that lutein modulates the expression of growth and survival-associated genes in prostate cancer cells.[87] In a meta-analysis conducted on 1958 subjects of oesophageal cancer, it was found that diet rich in carotenoids including lutein is directly related to lowering the risk of oesophageal cancer.[88] Another study conducted on 384 pancreatic cancer patients and 983 controls depicted that, diet rich in nutrients from fruits and vegetable sources, including lutein is beneficial to reduce the risk of pancreatic cancer patients showing a greater correlation (0.82).[89] Studies conducted in Washington (295 subjects), Sweden (201 subjects) and New York (270 subjects) to evaluate the relationship between plasma levels of lutein and breast cancer risk, have proven inverse relation between lutein concentration and breast cancer risk.[90]

Immuno modulation

Immunomodulation refers to any process in which an immune response is altered to a desired level. Microorganisms are also capable of modulating the response of the immune system to their presence, in order to establish or consolidate an infection.[91]

Dietary carotenoids have the ability of enhancing immune response, by increasing the phagocytic activity of macrophages. Lutein induces intracellular (reactive oxygen species) ROS generation and MAPK and RARβ (retinoic acid receptor) activation in macrophages, leading to an increase in matrix metalloproteinase 9 release and macrophage phagocytosis, this signifying the immunomodulatory effects.[92] Many authors have documented the immune modulatory effects of lutein in their animal studies, showing stimulatory effect of lutein on cell mediated and humoral response in animals. A study was conducted on 59 healthy students using the commercially available fruit and vegetable juice powder concentrate, which is rich in phytochemicals including lutein. This concentrate was consumed by students for a period of time and it was found that they had lesser symptoms than the placebo group and an increase in antioxidant activity and circulating gamma T cells (30%) was also found.[93]

Diabetes management

Diabetes is a group of metabolic diseases characterized by hyperglycaemia resulting from defects in insulin secretion, insulin action, or both. The chronic hyperglycaemia of diabetes is associated with long-term damage, dysfunction and failure of different organs, especially the eyes, kidneys, nerves, heart and blood vessels.[94]

Epidemiologic studies suggest that serum carotenoids including lutein are potent antioxidants and can prevent the chances of develop chronic diseases like diabetes. Randomized trials conducted in Queensland, Australia to study the relationship between carotenoids and diabetes proved that both are inversely related.[95] Lutein was also found to minimize the diabetes induced histological, biological and functional modifications.[96] In a population based study conducted on 133 diabetic patients, it was found that lutein and zeaxanthin showed a protective effect against hyperglycemia.[97] Effect of lutein was also studied for development of diabetic complications in rats. It was found that lutein having antioxidant properties, was able to prevent such complications.[98]

Skin health

Human skin is naked and is constantly directly exposed to the air, solar radiation, other environmental pollutants, or other mechanical and chemical insults, which are capable of inducing the generation of free radicals as well as reactive oxygen species (ROS) of body's own metabolism. ROS are generated during normal metabolism, are an integral part of normal cellular function and are usually of little harm because of intracellular mechanisms that reduce their damaging effects.[99]

The antioxidant property of lutein is known to protect the skin from oxidation. The protection mechanisms involve both quenching of singlet oxygen and of damaging free radicals. Lutein and zeaxanthin have been reported to help in protecting the skin against ultraviolet irradiation-induced damage.[100,101] Nutri-cosmetics and cosmeceuticals available commercially as beauty pills or oral cosmetics are composed of antioxidants like lutein thus having antiaging effect.[102] Some in vitro studies have also proved the efficiency of lutein as photo protectors, they protect the skin against sunburn (solar erythema) by increasing the basal defence against UV light-mediated damage.[103] In a clinical trial designed to study the effects of lutein in skin upon five skin physiology parameters (surface lipids, hydration, photo protective activity, skin elasticity and skin lipid peroxidation - malondialdehyde) of human subjects, the results showed that it provides the highest degree of antioxidant protection.[104] In another study conducted on 50 subjects affected by dry skin, lutein supplements proved out to be beneficial and resulted in a decrease in 40% of oxidative stress when measured by various vision surveillance tests.[105] Authors have also documented lutein as one of naturally occurring carotenoids with antioxidative, antitumorigenic, antiangiogenic, photoprotective, hepatoprotective, and neuroprotective properties.[106,107]

Cognitive health

"The eye and the brain are connected, so it's no surprise lutein is important for brain health." Dr. Dick Roberts.

Lutein is the predominant carotenoid in human brain tissue. Lutein and zeaxanthin in neural tissue may have biological effects that include antioxidation, anti-inflammation and structural actions. In adults, higher lutein status is related to better cognitive performance, and lutein supplementation improves cognition.[108] A study was conducted on 35 community dwelling older adults ages 65-94 engaged in an fMRI adapted verbal paired associates (VPA) task, including a learning and recalling test. Lutein/zeaxanthin levels were estimated using a standard Macular Pigment Ocular Density (MPOD) procedure and used as a covariate in the fMRI analyses. The results showed that subjects with lower lutein levels might have compensated neural mechanisms to help them in learning and recalling process.[109] Another study conducted in 36 subjects of Alzheimer's disease and 33 controls and comparing their macular pigments, concluded that the subjects with the disease had significantly lower levels of lutein as compared to the controls.[110]

Lutein is the predominant carotenoid in paediatric and adult brain tissue. In infant brains, the relative contribution of lutein to the total carotenoids is twice that found in adults, accounting for more than half of the concentration of total carotenoids. Therefore, the greater proportion of lutein in the paediatric brain suggests a need for lutein during neural development. Infant formula is not routinely supplemented with lutein, whereas breast milk is a highly bioavailable source of lutein. The evidence to date warrants further investigation into the role of lutein and zeaxanthin in visual and cognitive health throughout the lifespan.[1]

Conclusion and future recommendations

Lutein and zeaxanthin are xanthophyll carotenoids found particularly in dark-green leafy vegetables and in egg yolks. They are widely distributed in tissues and are the principal carotenoids in the eye lens and macular region of the retina. Epidemiologic studies indicating an inverse relationship between xanthophyll intake (or) status and both cataract and age-related macular degeneration suggest that these compounds can play a protective role in the eye. Some observational studies have also shown these xanthophylls may help reduce the risk of certain types of cancer, particularly those of the breast and lung. Emerging studies suggest a potential contribution of lutein and zeaxanthin to the prevention of heart disease and stroke.

Since the benefits of lutein as a nutritional supplement has been explored in recent years, its application as a nutraceutical needs to be exploited, especially in food industries.

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