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Lycopene and Lutein; A review for their Chemistry and Medicinal Uses

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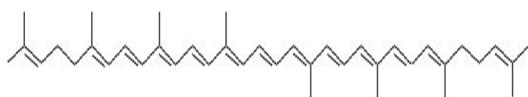
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Lycopene and lutein are important carotenoids. These are found to be very beneficial for maintaining a good health. This review discuss in details the medicinal uses of lycopene specially antioxidant and anticancer activities, besides other important effects. The most characteristic medicinal uses of lutein are its uses in ocular conditions specially cataract.

Keyword: Lycopene, Lutein, Medicinal Uses, Chemistry.

1. Introduction

1.1 Lycopene



Lycopene: ψ, ψ -Carotene

Formula: C₄₀H₅₆,

Mol.wt (average): 536.873

Melting point: 176°C^[1].

Lycopene is not a necessary nutrient. However, like other substances found in fruits and vegetables, it may be very important for optimal health.

1.2 Color

Lycopene is a natural constituent of red fruits and vegetables and of certain algae and fungi^[2].

1.3 Source

Tomatoes and tomato-based products are the major and the best sources of lycopene in the human diet. In analogy to other carotenoids, lycopene occurs in various geometrical configurations. Lycopene present in fresh tomatoes consists predominantly of all-*trans*-lycopene^[3]. Happily, cooking doesn't destroy lycopene, so pizza sauce is just as good as a fresh tomato. In fact, some studies indicate that cooking tomatoes in oil may provide lycopene in a way that the body can use better^[2,4], although not all studies agree^[5]. Lycopene is also found in watermelon, pink guava, apricot, papaya and pink grapefruit. Synthetic lycopene is also available,

and appears to be as well absorbed as natural-source lycopene^[6].

1.4 Medicinal uses

▪ Antioxidant

Biological activities of lycopene are antioxidant activity (singlet oxygen quenching and peroxy radical scavenging), induction of cell-cell communication, and growth control, but no provitamin A activity^[7].

Lycopene is the major carotenoid in tomatoes. Tomatoes contain a matrix of many bioactive components, including vitamin C, vitamin E, other carotenoids (α -, β -, γ - carotene, lutein), and flavonoids. Their synergistic interactions, when used in combination, may be responsible for the observed beneficial effects of tomato-based products. This study investigated the synergistic antioxidant activity of lycopene in combination with β -carotene, vitamin E, and lutein. A liposome system was used to test the synergistic antioxidant activity. The carotenoid mixtures were more efficient in protecting liposome from oxidation than the individual carotenoid. Mixtures of lycopene and vitamin E appear to have the greatest synergistic antioxidant activity^[8].

The many conjugated double bonds of carotenoids make them potentially powerful antioxidants, and lycopene is no exception. Indeed, lycopene had the strongest singlet oxygen-quenching capacity of several carotenoids, with α -carotene, β -carotene, and lutein next in capacity. The weakest singlet oxygen quencher of the antioxidants studied was α -tocopherol, which is found in much greater concentrations in many body systems^[9].

▪ Cancer

Levy *et al.* have shown that lycopene is more potent than α and β -carotene in inhibiting the cell growth of various human cancer cell lines^[10]. The inhibitory effect of tomato juice rich in lycopene (17 ppm) was observed in rat colon carcinogenesis model^[11].

The tomato juice containing lycopene decreased the numbers, but not incidences, of urinary bladder transitional cell carcinomas in male

rats^[12]. Lycopene (50 ppm in drinking water) had inhibitory effect on lung carcinogenesis in male mice^[13]. Long-term (6 to 76 weeks of age) administration of a diet containing 0.005% lycopene did not reduce the risk of hepatocarcinogenesis in a rat spontaneous liver carcinogenesis model^[14].

Lycopene had anticarcinogenic activities in mammary gland, liver, skin and lung in mouse models, and also inhibited the development of aberrant crypt foci in rat colon^[15]. The moderate dose of α - and β -carotenes and lycopene enhanced gap-junctional intercellular communication^[16]. Both lycopene and β -carotene showed no inhibitory effect on the development of rat urinary bladder carcinomas, while combination of carotenoids with NSAID decreased numbers and incidences of cancers^[17].

Lycopene has also shown promise for leukoplakia, a precancerous condition of the mouth and other mucous membranes. In a double-blind, placebo-controlled study, 58 people with oral leukoplakia received either 8 mg oral lycopene daily, 4 mg daily, or placebo capsules for three months^[18]. Participants were then followed for an additional two months. The results indicated that lycopene in either dose was more effective than placebo for reducing signs and symptoms of leukoplakia, and that 8 mg daily was more effective than 4 mg.

1.5 Prostate cancer

A pilot study suggests that a tomato extract containing lycopene and other tomato carotenoids and phytochemicals may have a potential role in the treatment of prostate cancer^[19].

Lycopene in concert with other tomato carotenoids may be responsible for the observed protective effect against prostate cancer. While the chemoprevention and early stage treatment of prostate cancer with purified lycopene in clinical trials should be investigated, the collective protective effect of other tomato carotenoids cannot be overlooked^[20].

Consumption of lycopene, a carotenoid without provitamin A activity, has been associated with a lower risk of prostate and breast cancer^[21].

And the increased consumption of tomato products and other lycopene-containing foods might reduce the occurrence or progression of prostate cancer^[22].

Increasing evidence suggests that a single serving of tomatoes or tomato products ingested daily may contribute to protect from DNA damage. As DNA damage seems to be involved in the pathogenesis of prostate cancer, the regular ingestion of tomatoes or tomato products might prevent the disease^[23].

1.6 lycopenes decrease the expression of 5[alpha]-reductase inhibitor in prostate tumors in the rat MatLyLu Dunning prostate cancer model^[24].

▪ Pregnancy

The best study of lycopene thus far evaluated its possible benefits for pregnant women^[25]. Participants in this double-blind study of 251 women received either placebo or 2 mg of lycopene twice daily. For reasons that are not at all clear, use of lycopene appeared to reduce risk of preeclampsia, a dangerous complication of pregnancy. In addition, use of lycopene appeared to help prevent inadequate growth of the fetus. However despite these promising results researchers are cautious about drawing conclusions: several other nutritional substances have shown promise for preventing preeclampsia in preliminary trials only to fail when larger and more definitive studies were done^[26].

▪ Smoking

Peng et al^[27] found that plasma concentrations of β -carotene, α -carotene, lutein, zeaxanthin, cryptoxanthin, and *cis*- β -carotene, but not lycopene, were lower in smokers than in nonsmokers even at the same level of intake. In another study, Brady et al^[28] found that serum lycopene was not significantly lower in smokers than in nonsmokers, even though dietary intake of lycopene was lower in smokers. Rao and Agarwal^[29] also reported that serum lycopene concentrations did not differ significantly between nonsmokers and habitual smokers. In a sample of men aged 25–55 y, no significant differences in plasma lycopene concentrations

were observed between smokers, tobacco chewers, and nonusers^[30]. Hininger et al^[31] also found no significant difference in plasma lycopene concentrations between a sample of 11 smokers and 11 non-smokers. Thus, there is evidence that smoking status is not inversely related to circulating concentrations of lycopene in humans^[32].

▪ Other effects

The hydrocarbon carotenoids, including β -carotene and lycopene, are transported primarily in LDL, which puts them in prime position to protect LDL from oxidation^[33]. Gomez-Aracena et al^[34] found that the risk of myocardial infarction was 60% lower (odds ratio: 0.39, 95% CI: 0.13, 1.19; *P* for trend: 0.04) for the highest quintile of adipose lycopene concentration than for the lowest quintile after adjustment for age, family history of coronary heart disease, and cigarette smoking. Men with the highest concentrations of lycopene in their adipose tissue biopsy had a 48% reduction in risk of myocardial infarction when they were compared with men with the lowest adipose lycopene concentrations^[35]. For each quintile increase in lycopene concentration, there was a significant decrease in myocardial infarction risk. This association was partially masked by β -carotene concentrations. When there was simultaneous control for the 3 primary carotenoids, lycopene was the carotenoid with the major effect^[32].

Lycopene supplementation does not appear to have a beneficial effect on bronchodilation in young athletes who suffer from EIA symptoms and who demonstrate airway obstruction following exercise but are not under regular mediation^[36].

In addition, lycopene and related tomato carotenoids are also present at biologically significant concentrations in human retinal pigment epithelium [RPE/choroid], and ciliary body and may protect these tissues against oxidative damage to maintain the health and proper function of the human eye^[20].

1.7 Spectral Data for lycopene

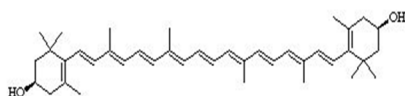
UV: λ_{\max} (nm): methanol 293, 360, 442, 468, 499^[37].

NMR: ¹H-NMR δ (CDCl₃): 5.11 (2, 2'-H), ca. 2.11 (3, 3'-H₂), ca. 2.11 (4, 4'-H₂), 5.95 (6, 6'-H), 6.49 (7, 7'-H), 6.25 (8, 8'-H), 6.18 (10, 10'-H), 6.64 (11, 11'-H), 6.35 (12, 12'-H), 6.25 (14, 14'-H), 6.62 (15, 15'-H), 1.688, 1.612 (1, 1'-gem-Me), 1.818 (5, 5'-Me), 1.968 (9, 9', 13, 13'-Me)^[38].

¹³C-NMR δ (CDCl₃): 131.64 (1, 1'), 124.12 (2, 2'), 26.83 (3, 3'), 40.30 (4, 4'), 139.30 (5, 5'), 125.94 (6, 6'), 124.87 (7, 7'), 135.54 (8, 8'), 136.15 (9, 9'), 131.64 (10, 10'), 125.21 (11, 11'), 137.46 (12, 12'), 136.54 (13, 13'), 132.71 (14, 14'), 130.17 (15, 15'), 25.66, 17.70 (1, 1'-gem-Me), 16.97 (5, 5'-Me), 12.90 (9, 9'-Me), 12.81 (13, 13'-Me)^[38].

Mass spectra m/z: 536 (M, 22%), 467 (M-69), 444 (M-92), 430 (M-106), 378 (M-158), 361 (M-106-69)^[39,40]
FD-MS m/z: 536^[41].

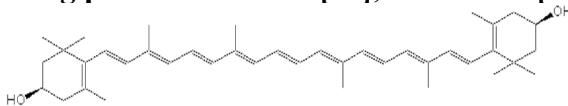
1.9 Lutein



Lutein: (3R,3'R,6'R)- β,ϵ -Carotene-3,3'-diol

Formula: C₄₀H₅₆O₂, **Mol. Wt (average):** 568.871

Melting point: 183-185°C [42], 174-178°C [43].



zeaxanthin: (3R,3'R)- β,β -Carotene-3,3'-diol

Formula: C₄₀H₅₆O₂ **Mol. Wt (average):** 568.871

Melting point: 207-208°C^[44].

Lutein and zeaxanthin belong to the xanthophyll family of carotenoids and are the two major components of the macular pigment of the retina^[45]. Lutein and zeaxanthin differ from other carotenoids in that they each have two hydroxyl groups, one on each side of the molecule. Zeaxanthin is a stereoisomer of lutein, differing only in the location of a double bond in one of the hydroxyl groups. The hydroxyl groups appear to control the biological function of these two xanthophylls^[46].

The two major carotenoids in the human macula and retina are lutein and zeaxanthin, and they are often referred to as xanthophylls, or macular pigment. Handelman *et al* found a fivefold higher content of these carotenoids in the macula compared with the peripheral retina^[47].

Source: Lutein and zeaxanthin are especially concentrated in leafy green vegetables, many

fruits, and colored vegetables such as sweet peppers, sweet corn, and peas and egg yolk^[47].

Maize was the vegetable with the highest quantity of lutein (60% of total) and orange pepper was the vegetable with the highest amount of zeaxanthin (37% of total). Substantial amounts of lutein and zeaxanthin (30–50%) were also present in kiwi fruit, grapes, spinach, orange juice, zucchini (or vegetable marrow), and different kinds of squash^[47].

Color: Bright yellow

1.10 Medicinal uses

However, lutein is structurally related to α -carotene and zeaxanthin to β -carotene. Therefore, they have different preferences for interaction with membrane structures, with theorized differences in local function. Despite their structural similarities to α -carotene and β -carotene, they are not provitamin A carotenoids. The 5 major serum carotenoids are lycopene, β -carotene, α -carotene, lutein, and zeaxanthin. Approximately 30 to 50 carotenoids may exist in the diet, and about 20 may be measurable in the serum. The fact that only 2 of these, lutein and zeaxanthin, are present in the retina leads us to question why^[48].

▪ Ocular Conditions

The macular pigment (MP) is composed predominantly of lutein (L) and zeaxanthin (Z)^[49], and is of dietary origin^[50]. Lutein appears to have an affinity for the peripheral retina and rods, while zeaxanthin seems to be preferentially taken up by the cones of the macula^[51].

These carotenoids can be found in various body tissues; however, their concentration is highest in the macula in the photoreceptor axons. The MP has band-pass spectral absorption characteristics with peak absorption at 460 nm, thus acting as a pre-receptor filter that selectively absorbs blue light^[52].

The macular region of the primate retina is yellow in color due to the presence of the macular pigment, composed of two dietary xanthophylls, lutein and zeaxanthin, and another xanthophyll, meso-zeaxanthin. The latter is presumably

formed from either lutein or zeaxanthin in the retina. By absorbing blue-light, the macular pigment protects the underlying photoreceptor cell layer from light damage, possibly initiated by the formation of reactive oxygen species during a photosensitized reaction. There is ample epidemiological evidence that the amount of macular pigment is inversely associated with the incidence of age-related macular degeneration, an irreversible process that is the major cause of blindness in the elderly. The macular pigment can be increased in primates by either increasing the intake of foods that are rich in lutein and zeaxanthin, such as dark-green leafy vegetables, or by supplementation with lutein or zeaxanthin. Although increasing the intake of lutein or zeaxanthin might prove to be protective against the development of age-related macular degeneration, a causative relationship has yet to be experimentally demonstrated^[53].

Age-related Macular Degeneration In older Americans, age-related macular degeneration (AMD) is the leading cause of blindness. It is characterized by atrophy of the macular disk. The retinal pigmented epithelium and photoreceptors (particularly the rods and the blue-light sensitive cones) are the most affected. It was found that a 57-percent decreased risk for AMD in individuals with the highest intake of lutein/zeaxanthin (6 mg daily), compared to those who consumed the lowest level (0.5 mg daily)^[54-56].

A hypothesis supposed that lutein and zeaxanthin are thought to protect the eye in two ways. One is that the macular pigment filters blue light, which is particularly damaging to photoreceptors and to the retinal pigment epithelium, and lutein and zeaxanthin absorb blue light. The second hypothesis is that these carotenoids act as antioxidants to limit the oxidant stress of the tissue that results from metabolism and light. It has been shown that one of the ways light damages the retina is by generation of free radicals that lead to peroxidation of membrane lipids. Carotenoids have long been known as powerful antioxidants.

Supplementation with a combination of L (10 mg day)⁻¹ and Z (10 mg day)⁻¹ over a period of 6 months increases MP distribution over $\pm 8^\circ$

around the macula, causing an almost uniform reduction in the percentage of transmitted blue light over the centre $\pm 4^\circ$ ^[52].

▪ **Cataracts**

Lutein and zeaxanthin are the only two carotenoids that have been identified in the human crystalline lens. Like the antioxidant enzymes found N.I. Krinsky, E.J. Johnson / *Molecular Aspects of Medicine* 26 (2005) 459–516 497 within the lens, the lipid-based lutein and zeaxanthin, are primarily found in the metabolically active epithelium/outer cortex of the lens, and therefore, may have a preferential role in protecting against UV-induced oxidative damage. This function would be similar to the role that lutein and zeaxanthin play in the retina, where they are optimally located to reduce risk from blue light.

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^[57]. 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. These studies provide strong evidence for a protective role for lutein/zeaxanthin against development of cataracts^[58-59].

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^[60].

In a recent report, it was observed in women that those with the highest intake of lutein and zeaxanthin had a 22% decreased risk of cataract extraction compared with those in the lowest quintile. It was also observed that there was a lower risk of cataract extraction in men with higher intakes of lutein and zeaxanthin but no other carotenoids. In this study, men in the highest fifth of lutein and zeaxanthin in the lowest fifth.

■ Other effects

Lutein had an Inhibitory effect on Epstein-Barr virus activation (anti-tumor promotion)^[61], Inhibitory effect on colonic aberrant crypt foci formation (anti-tumor promotion)^[62]. Lutein showed the anti-tumor promoting activities in mouse two-stage skin carcinogenesis and decreased the number of aberrant crypt foci in rat colon^[63]. Lutein decreased the number of aberrant crypt foci in colons in mice^[64]. Lutein and suppressed tumorigenesis in skin and colon in mice^[65].

A membrane-associated xanthophyll-binding protein, which is a Pi isoform of human glutathione S-transferase (GSTP1), is purified from human macula. It binds (3R, 3'R)-zeaxanthin and (3R,3'S-meso)-zeaxanthin, but not lutein A^[14].

Crystal structure of spinach major light-harvesting complex (LHCII) contains 2 lutein, 1 9'-cis neoxanthin, 1 (violaxanthin, antheraxanthin or zeaxanthin), 8 chlorophyll a, and 6 chlorophyll b per monomer^[67].

1.11 Zeaxanthin

It has a reinforcement effect of phospholipid bilayer^[68], Inhibitory effect on Epstein-Barr virus activation (anti-tumor promotion)^[61]. Zeaxanthin inhibited the development of mouse spontaneous liver cancer^[69]. It showed anticarcinogenic activity in liver in mice^[70].

(3R,3'R)-Zeaxanthin, meso-zeaxanthin and (3R, 3'R,6'R)-lutein are located in human macula^[71,72]. A membrane-associated xanthophyll-binding protein, which is a Pi isoform of human glutathione S-transferase

(GSTP1), is purified from human macula. It binds (3R, 3'R)-zeaxanthin and (3R, 3'S-meso)-zeaxanthin, but not lutein A^[73]. A water-soluble surface-associated complex from *Prochlorothrix hallandica* composed of two polypeptides of 56 and 58 kDa, zeaxanthin and lipopolysaccharide^[74].

1.12 Spectral Data for Lutein

- UV:** λ_{\max} (nm): (ϵ): dioxane 429 (1680), 453 (2515), 482 (2259)^[75] methanol 330, 422 (shoulder), 443, 470^[76].
- NMR: 1H-NMR δ :** 1H-NMR δ (270 MHz, CDCl₃): 0.849, 0.998 (6H, s, 1'-gem-Me), 1.074 (6H, s, 1-gem-Me), 1.37 (1H, dd, J 13, 7, 2'ax-H), 1.48 (1H, t, J 12, 2ax-H), 1.626 (3H, s, 5'-Me), 1.739 (3H, s, 5-Me), 1.84 (1H, dd, J 13, 6, 2'eq-H), 1.912 (3H, s, 9'-Me), 1.970 (9H, s, 9-, 13-, 13'-Me), 2.04 (1H, dd, J 17, 10, 4ax-H), ca. 2.33-2.45 (2H, m, 6'-, 4eq-H), ca. 4.0 (1H, m, 3-H), 4.25 (1H, 3'-H), 5.43 (1H, dd, J 15.5, 10, 7'-H), 5.55 (1H, s, 4'-H), ca. 6.12 (2H, s, 7-, 8-H), ca. 6.15 (3H, m, 8'-, 10-, 10'-H), ca. 6.26 (2H, m, 14-, 14'-H), 6.36 (2H, d, J 15, 12-, 12'-H), ca. 6.55-6.71 (4H, m, 11-, 11'-, 15-, 15'-H)^[75,77,78].
- 13C-NMR δ** (CDCl₃): 13C-NMR δ (CDCl₃): 37.1 (C1), 48.4 (C2), 65.1 (C3), 42.5 (C4), 126.2 (C5), 137.6 (C6), 125.6 (C7), 138.5 (C8), 135.6 (C9), 131.3 (C10), 124.9 (C11), 137.6 (C12), 136.5 (C13), 132.6 (C14), 130.0 (C15), 28.7, 30.2 (1-gem-Me), 21.6 (5-Me), 12.7 (9-Me), 12.7 (13-Me), 34.0 (C1'), 44.7 (C2'), 65.9 (C3'), 125.6 (C4'), 137.8 (C5'), 55.0 (C6'), 128.6 (C7'), 137.8 (C8'), 135.0 (C9'), 130.8 (C10'), 124.5 (C11'), 137.6 (C12'), 136.5 (C13'), 132.6 (C14'), 130.0 (C15'), 24.3, 29.5 (1'-gem-Me), 22.8 (5'-Me), 13.2 (9'-Me), 12.7 (13'-Me)^[79].

1.13 Spectral Data for Zeaxanthin

- UV:** λ_{\max} (nm): (ϵ): hexane 452 (133692), 480 (116624)⁸⁰ methanol 275, 341, 429 (shoulder), 448, 473^[81].
- NMR: 1H-NMR δ** 1H-NMR δ (CDCl₃): 1.48 (2, 2'ax-H), 1.77 (2,2'eq-H), ca. 4.00 (3, 3'-H), 2.04 (4, 4'ax-H), 2.39 (4,4'eq-H), 6.11 (7, 7'-H), 6.13 (8, 8'-H), 6.16 (10, 10'-H), 6.64 (11, 11'-H), 6.36 (12, 12'-H), ca. 6.26 (14, 14'-H), ca. 6.63 (15, 15'-H), 1.074 (1, 1'-gem-Me), 1.736 (5, 5'-Me), 1.967, 1.972 (9, 9', 13, 13'-Me), ca. 1.35 (OH)^[82].
- 13C-NMR δ** (CDCl₃): 13C-NMR δ (CDCl₃): 37.1 (1, 1'), 48.2 (2, 2'), 65.1 (3, 3'), 42.4 (4, 4'), 126.1 (5, 5'), 137.6 (6, 6'), 125.5 (7, 7'), 138.5 (8, 8'), 135.7 (9, 9'), 131.3 (10, 10'), 124.9 (11, 11'), 137.6 (12, 12'), 136.5 (13, 13'), 132.6 (14, 14'), 130.0

(15, 15'), 28.7, 30.2 (1, 1'-gem-Me), 21.7 (5, 5'-Me), 12.8 (9, 9'-Me), 12.8 (13, 13'-Me)^[79].

4. **Mass spectra:** m/z: 568 (M, 100%), 550 (M-18, 84%), 532 (M-18-18, 5%), 489 (M-79, 1%), 476 (M-92, 13%), 462 (M-106, 1%), 458 (M-18-92, 11%), 444 (M-18-106, 1%), 410 (M-158, 5%)^[83,84], FD-MS m/z: 568^[85].

2. Conclusion

Lutein and lycopene are naturally occurring substances found in many plants. Carotenoids in general have undergone a number of research studies as to their possible benefits against diseases, among other health issues. Lycopene is considered as antioxidant and anticancer agents while lutein showed marked effects on ocular conditions specially cataract. Lutein is particularly being studied for its effects on the human eyes. Lutein and lycopene are both found in numerous foods.

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