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Exploring the role of lutein in eye health

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Abstract

Lutein, a xanthophyll carotenoid, has gained significant attention for its potent antioxidant and anti-inflammatory properties, particularly in protecting eye health. Derived from dark green leafy vegetables like spinach and kale, lutein is known for its ability to neutralize harmful free radicals and reduce blue light-induced phototoxic damage in the retina. Research has demonstrated that lutein, through dietary intake, accumulates in the macula, a critical part of the retina, where it, along with zeaxanthin and meso-zeaxanthin, forms the macular pigment, essential for visual function. Studies highlight its effectiveness in lowering the risk of age-related macular degeneration (AMD), as evidenced in the AREDS2 study, and enhancing macular pigment density. Additionally, lutein's role in diabetic retinopathy is emerging, with experimental models showing reduced retinal oxidative stress and improved visual outcomes following supplementation. Although epidemiological data on lutein's impact on diabetic retinopathy are limited, initial findings suggest its potential therapeutic benefits. The mechanisms by which lutein exerts these effects include neutralizing reactive oxygen species (ROS), filtering blue light, inhibiting the pro- inflammatory cytokine cascade, and regulating the complement system. Overall, lutein's role in preventing AMD, cataracts, and potentially diabetic retinopathy underscores the importance of adequate dietary intake or supplementation for maintaining optimal eye health.

Keywords: Lutein; Antioxidant; Age-related macular degeneration (AMD); Carotenoids; Retinal health; Blue light; Diabetic retinopathy; Macular pigment

1. Introduction

A substantial amount of research indicates that a diet high in antioxidants, known for their anti-inflammatory properties [1, 2], may help alleviate the impact of chronic diseases.

[3] In recent years, growing interest has focused on the health benefits of carotenoids. A high dietary intake of these compounds has been linked to positive effects on various systemic diseases [4] and eye disorders, particularly by safeguarding the retina from phototoxic light damage. [5] The majority of research has concentrated on lutein (L), a carotenoid with potent antioxidant properties in vitro [6], which has been linked to a lower risk of age-related diseases. [7]

Lutein, a member of the xanthophyll carotenoid family, is naturally synthesized in dark green leafy vegetables like spinach and kale.[8,9] The average daily intake of lutein in the American diet is around 1.7 mg.[10] Its purified crystalline form is generally recognized as safe for inclusion in food and beverages.[11] Lutein is absorbed in the gastrointestinal tract with fats and transported via lipoproteins, with apolipoprotein E playing a role in its serum transport.[12] The majority of lutein is carried by High-Density Lipoproteins (HDLs) (52%) and Low- Density Lipoproteins (LDLs) (22%).[13] In the presence of cholesterol, lutein tends to separate from saturated lipid regions (liquid- ordered phase) in cell membranes, accumulating instead in unsaturated phospholipids to form carotenoid-rich

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domains.[14] Tissue-specific concentrations of lutein depend on dietary intake [15,16], with approximately 0.2 μM circulating throughout the body after ingestion. Lutein is directed to target tissues such as the retina, where it plays a key role in maintaining tissue homeostasis. [10]

2. Characteristics of lutein

2.1. Chemical structure

The biochemistry and metabolism of lutein have been thoroughly reviewed recently. [17] In summary, lutein is a carotenoid. Carotenoids are composed of a 40-carbon skeleton, formed by the head-to-head joining of two 20-carbon precursors, geranylgeranyl pyrophosphate (GGPP). This long carbon skeleton contains conjugated double bonds arranged in linear and cyclic forms, allowing for structural variations, such as cis or trans configurations.[19] Carotenoids that consist solely of hydrocarbons are classified as carotenes, while those with at least one oxygen atom in their polyene chain are categorized as xanthophylls. Lutein is part of the xanthophyll subgroup, characterized by two hydroxyl groups attached to its terminal ionone rings on both ends. [18]

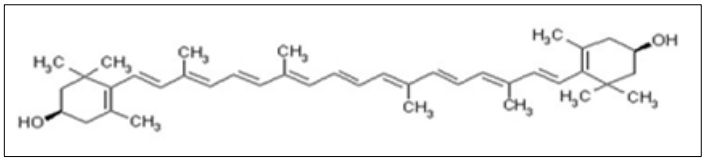

Figure 1 Chemical structure of lutein

2.2. Absorption and metabolism

As mentioned earlier, mammals cannot synthesize carotenoids, so they must be obtained through dietary intake. [20] Once consumed, lutein (L) is absorbed in the small intestine's mucosa, where it binds to chylomicrons and is then secreted into the lymphatic system before reaching the liver.[21] In the liver, lutein is incorporated into lipoproteins, which transport it to peripheral tissues,[35,36] particularly the retina, where the highest concentrations have been observed. [22] Being fat-soluble, [23] lutein's absorption is facilitated by dietary lipids, as it is incorporated into micelles. [24] Various dietary factors can influence lutein absorption. For instance, a fiber-rich diet has been shown to lower carotenoid serum levels, [25, 26] thereby affecting lutein uptake. Additionally, the presence of other carotenoids in the diet may compete with lutein for absorption. [27] Nutrients such as iron and zinc, as well as protein deficiencies, can also impact lutein absorption.[28] Conversely, the presence of mono- and di- glycerides has been linked to improved lutein absorption, as evidenced by increased plasma lutein levels.[29] Furthermore, non-dietary factors may reduce lutein bioavailability. For example, orlistat, a drug that inhibits lipase activity, has been shown to decrease lutein absorption,[30] similar to the effect of impaired pancreatic enzyme activity,[31] as observed in patients with cystic fibrosis,[32] and to a lesser extent, smoking[33] and alcohol consumption.[34]

2.3. Distribution

Lutein is unevenly distributed among human tissues, with the highest concentration found in the macula, a region in the central retina responsible for sharp, central vision due to its abundance of photoreceptor cells. Alongside lutein, two other carotenoids are present in the macula: zeaxanthin, a dietary stereoisomer of lutein, and meso-zeaxanthin, a metabolite of lutein produced in the macula. [37] These carotenoids are distributed in specific regions within the macula: lutein dominates the periphery, zeaxanthin the mid- periphery, and meso-zeaxanthin the center. [38] Together, they form the retinal macular pigment, which is critical for optimal visual function and is often used as an indicator of macular disease risk. [39]

Recent research using confocal resonance Raman microscopy has further detailed the spatial distribution of lutein and zeaxanthin in the retina. It was found that zeaxanthin is most concentrated in the fovea and decreases sharply in the peripheral macula, while lutein is more evenly distributed at lower levels across the macula.[40] Lutein is also present in the human lens, where it helps protect against age-related eye conditions such as cataracts.[41] Additionally, studies suggest that lutein's hydrophobic nature leads to its storage in adipose tissue, and this can reduce retinal lutein levels in obese individuals, potentially increasing their risk of eye diseases.[42]

2.4. Mechanism of action

Animal and in vitro studies have shown that certain carotenoids possess antioxidant properties.[43,44] Lutein, in particular, has been proven to exhibit strong antioxidant effects by neutralizing singlet oxygen and scavenging free radicals,[45,46] though it is considered less potent in this regard compared to zeaxanthin.[45] Another key protective role of lutein is its ability to filter blue light, thereby reducing phototoxic damage to photoreceptor cells.[47] Subczynski et al. suggested that lutein's protective effects may be enhanced by its strategic localization in the retina's most vulnerable areas and its specific membrane orientation.[48] Additionally, lutein has been shown to inhibit the pro-inflammatory cytokine cascade[49] and the transcription factor nuclear factor-kB (NF-kB).[50-52] Evidence also supports lutein's role in reducing reactive oxygen species (ROS) production,[50,53] decreasing the expression of inducible nitric oxide synthase (iNOS), [54] and modulating the activation of the complement system. Through these mechanisms, lutein likely plays a crucial role in regulating immune responses, modulating inflammation, and minimizing oxidative damage.

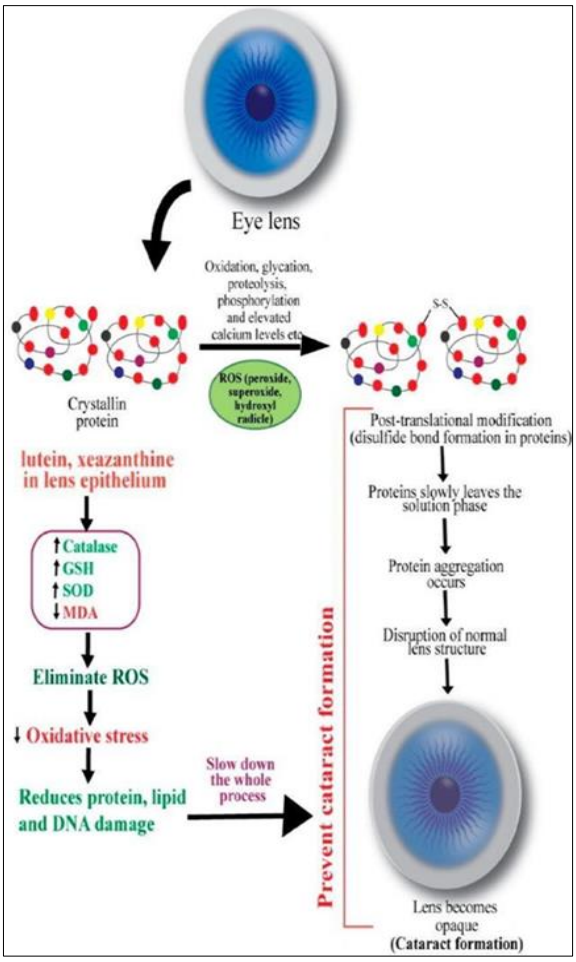

Figure 2 Mechanism of action of lutein

3. Role of Lutein in Age-Related Macular Degeneration (AMD)

Lutein, a carotenoid with potent antioxidant properties, has been extensively studied in the context of Age-Related Macular Degeneration (AMD), a leading cause of blindness in older adults. The research on lutein's role in AMD consists of both experimental studies (focusing on cellular mechanisms, animal models, and clinical trials) and epidemiological studies (analyzing population-based data).

3.1. Experimental Studies

3.1.1. Antioxidant Protection in Retinal Cells

- Study: Khachik et al. (2006) explored the protective effects of lutein and zeaxanthin on human retinal pigment epithelial cells exposed to oxidative stress.
- Findings: Lutein reduced the amount of lipid peroxidation in retinal cells, which is crucial as oxidative stress and lipid peroxidation are key contributors to AMD progression.[55]

3.1.2. Animal Model Studies

- Study: Ozawa et al. (2012) used mouse models to investigate the role of lutein in protecting against photoreceptor cell death induced by light damage.
- Findings: Lutein supplementation in mice significantly reduced photoreceptor damage and maintained retinal function after exposure to blue light, which is relevant since blue light is a known contributor to AMD.[56]

3.1.3. Improvement of Macular Pigment Density

- Study: In a randomized controlled trial (RCT) by Richer et al. (2004), subjects with AMD were given lutein supplementation over a 12-month period.
- Findings: The trial demonstrated significant improvement in macular pigment optical density (MPOD) and visual function, showing lutein's direct impact on protecting and enhancing macular health.[57]

3.2. Epidemiological Clinical Studies

3.2.1. The AREDS2 Study

- Study: The Age-Related Eye Disease Study
- 2 (AREDS2) was a large, multicenter, randomized clinical trial designed to assess the impact of lutein and zeaxanthin supplementation in reducing the risk of AMD progression.
- Findings: AREDS2 found that replacing beta-carotene with lutein and zeaxanthin in supplementation formulations significantly reduced the progression of advanced AMD, particularly in individuals with low dietary intake of these carotenoids.[58]

3.2.2. Blue Mountains Eye Study

- Study: This large population-based cohort study evaluated the association between dietary intake of lutein and zeaxanthin and the risk of AMD in individuals over the age of 55.
- Findings: Higher dietary intake of lutein and zeaxanthin was associated with a lower risk of both early and late AMD, suggesting that lutein may have a protective role over time.[59]

3.2.3. The Carotenoids in Age-Related Eye Disease Study (CAREDS)

- Study: This epidemiological study assessed women's intake of lutein and zeaxanthin over a period of 15 years to examine its impact on AMD risk.
- Findings: Women with higher dietary intakes of lutein and zeaxanthin had significantly lower risks of developing intermediate and advanced stages of AMD compared to those with lower intake levels.[60]

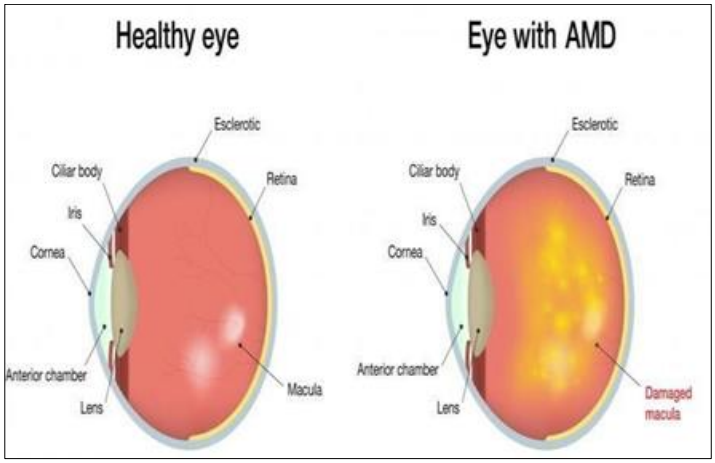

Figure 3 Carotenoids in Age-Related Eye Disease Study (CAREDS)

4. Lutein Role in Diabetic Retinopathy

4.1. Experimental Studies

Diabetic retinopathy can be induced in animal models using streptozocin, a compound that selectively destroys pancreatic β cells responsible for insulin production. In diabetic mice, this results in significant weight loss and elevated blood glucose levels. Consequently, retinal ganglion cells and amacrine cells in the inner nuclear layer (INL) undergo apoptosis. Studies have shown that lutein inhibits the formation of reactive oxygen species (ROS) in the retinas of diabetic mice and rats. ROS levels in the retina were measured using dihydroethidium, while visual function was assessed through electroretinograms. Notably, lutein administration restored the diminished oscillatory potential amplitudes observed in the diabetic mice.[61,62]

Epidemiological and Clinical Studies The role of lutein in diabetic retinopathy has been minimally explored in human studies. To date, only one prospective study by Hu et al. has investigated patients with non- proliferative diabetic retinopathy, revealing significantly lower serum levels of lutein and zeaxanthin in these patients compared to healthy individuals. The study further indicated that supplementation with lutein and zeaxanthin led to improvements in visual acuity and a reduction in foveal thickness. These findings suggest that lutein and zeaxanthin supplementation could serve as potential therapeutic agents for treating non- proliferative diabetic retinopathy.[62]

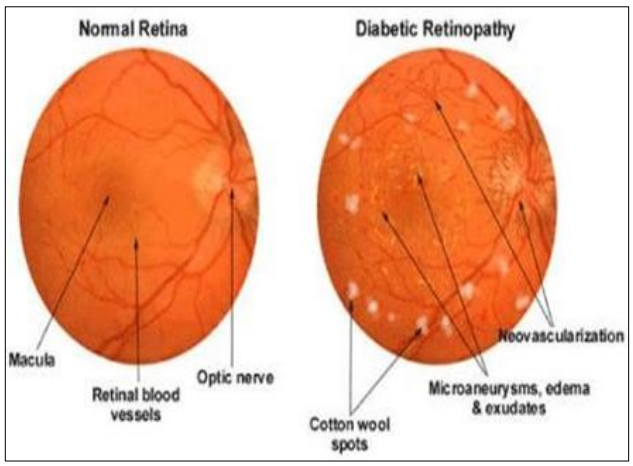

Figure 4 Lutein Role in Diabetic Retinopathy

5. Conclusion

Lutein, often referred to as the "eye vitamin," plays a crucial role in protecting against various eye diseases, particularly age-related macular degeneration (AMD) and cataracts. Its antioxidant, anti- inflammatory, and blue light-absorbing properties help safeguard the lens and retina, making adequate dietary intake essential for maintaining healthy levels of lutein in the eyes.

Compliance with ethical standards

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Disclosure of conflict of interest

There is no conflict of interest to be disclosed.

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