

## Perspective

# Lutein and Zeaxanthin: An Overview of Metabolism and Eye Health

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In 2010, 4.1 million Americans over age 40 were considered visually impaired (i.e. blind or with low vision) [1]. With almost one-third of these visually impaired affected by low vision, or sight in the better eye worse than 20/40 vision despite corrective lenses, low vision and vision loss are among the most feared irreversible diseases among the elderly and can reduce quality of life as well as incur serious economic burdens [1]. Age-related eye diseases such as diabetic retinopathy, glaucoma, and age-related macular degeneration (AMD) are the leading causes of visual impairment worldwide and together affect over 12.4 million Americans aged 40 or older [1]. Vision loss overtime is largely due to the irreversible loss of retinocytes, and subsequent degeneration of the retina of the eye, leading to AMD and other diseases [2]. While treatment is limited, nutritional interventions may be beneficial in improving eye health. Considerable research suggests an inverse relationship between carotenoids, polyunsaturated fatty acids, and some vitamins and the prevention or delay of progression of AMD and other age-related degenerative diseases.

Lutein (LUT) and zeaxanthin (ZEA) are two xanthophyll carotenoids found in dark green and yellow fruits and vegetables associated with retino protective properties. An average U.S. diet contains 1-3 mg/day of LUT and ZEA, while ~6 mg/day has been associated with lower risks of disease like AMD and cataracts [3]. It is proposed that the retino protective capabilities associated with these xanthophylls may be due to the unique chemical structure and selective retinal accumulation. Hydroxyl groups, large numbers of double bonds, and the polar nature of these compounds may contribute to LUT and ZEA's ability to protect against oxidative stress associated with AMD by scavenging free radicals and transferring energy states [4]. Intake of LUT and ZEA and their selective retinal accumulation may increase macular pigment density which may slow or prevent AMD [5]. LUT and ZEA are considered recent significant eye health research interests for these reasons.

The bioavailability and potential benefits of LUT and ZEA on eye health is dependent on the digestion, absorption, transport, retinal uptake, and storage of these carotenoids [6]. Multiple factors influence carotenoid bioavailability including the food matrix, processing conditions, and the fat content of the diet [7]. In general, carotenoids are fat soluble compounds and follow lipophilic digestion and absorption pathways. Traditionally, individuals diagnosed with AMD may be instructed to follow

low-fiber, low-fat diets; however these recommendations may be archaic. Recent findings suggest diets that provide foods with high glycemic indexes are positively associated with AMD risk, dietary fat consumption may significantly increase LUT bioavailability, and supplementation of xanthophylls with omega-3 fatty acids may decrease risk of AMD [8-10].

Upon ingestion, food is mechanically and enzymatically broken down, carotenoids are released with help from dietary lipids, emulsified in the small intestine and incorporated and solubilized into micelles for enterocyte absorption via passive diffusion or scavenger receptor class B type 1 (SR-B1)-facilitated diffusion. In the enterocyte, carotenoids are packaged into chylomicrons, transported to the liver, repackaged into lipoproteins and transported to extra hepatic tissues through the blood [11]. Along with LDL, HDL has been identified as a crucial xanthophyll transporter, and deficiencies in this lipoprotein may impair LUT and ZEA transport [12]. Although these xanthophylls may accumulate in hepatic, adrenal, adipose tissues, as well as others through various transport mechanisms, of greatest interest is the retinal accumulation and macular effect of these carotenoids [13].

LUT and ZEA make up about 80% of the total carotenoid content of the retina, a higher concentration than any other tissue of the human body [13,14]. LUT and ZEA, as well as meso-zeaxanthin (meso-ZEA), a LUT metabolite, accumulate as a yellow spot in the macula of the eye, known as the macular pigment. This pigment has been suggested to contain antioxidant-like properties, reduce photoreceptor exposure to blue light, and protect the macula from light-induced oxidative stress [14,15]. Generally, the ratio of the macular carotenoids varies in different regions in the eye. Amounts of LUT and ZEA tend to decrease from the fovea toward the periphery of the eye. In the fovea for example, less lutein is found compared to zeaxanthin, in a 1:2 ratio; however in the peripheral retina the ratio of LUT to ZEA is 2:1 [16]. As previously stated, higher intakes of LUT and ZEA have been associated with increased macular pigment densities. Significant research indicates that high macular pigment densities slow or prevent AMD, suggesting an inverse relationship between xanthophyll consumption and AMD [5]. Although the distribution of the macular pigment may vary, the transport governing the status, regulation, and function of these carotenoids in the retina remain unclear.

The retinal pigment epithelium (RPE) may be a transfer point

of LUT and ZEA from the blood to the neural retina portion of the eye, using specific xanthophyll-binding proteins (XBP) for retinal uptake and macular concentration [17]. Many XBPs have been identified; however the exact mechanism of LUT and ZEA uptake is ambiguous. Glutathione S-transferase (GSTP1), located in the macula preferentially interacts with ZEA and meso-ZEA, while more the steroidogenic acute regulatory domain 3 (StARD3) is partly responsible for retinal uptake of LUT [18,19]. Some research suggests that cell lines similar to RPE are involved in LUT and ZEA uptake and are entirely dependent on SR-B1 transporters [17]. Different research indicates that carotene cleavage oxygenases (CCOs) mediate site-specific cleavage of double bonds forming apo-carotenoid metabolites, which may have important metabolic roles that differ from the original compound [20]. Mein and associates demonstrated that xanthophyll cleavage enzyme carotene-9'10'-monooxygenase, (CMO2, also known as  $\beta,\beta$ -Carotene-9',10'-dioxygenase 2 or BCO2), a CCO highly expressed in the RPE, cleave LUT and ZEA at the 9,10 and 9',10' double bonds in ferrets [20]. No apo-carotenoid metabolites in the RPE have been identified from this BCO2 cleavage, however other LUT and ZEA metabolites have. The functional purpose of these metabolites remains elusive but includes: 3'-epilutein, 3-OH- $\beta$ ,  $\epsilon$ -caroten-3'-one and aforementioned meso-ZEA [21].

Most recently, BCO2 is suggested as the underlying reason for human retinal accumulation of LUT and ZEA because of the enzyme inactivity or loss of enzymatic function [22], likely due to excess amino acid residues, GKAA. It is suggested that because human BCO2 has a weaker binding affinity for carotenoids when compared to mouse BCO2; this inability to capture macular carotenoids may be the grounds behind the human enzyme's loss of function. This loss of enzymatic function therefore prevents xanthophyll cleavage and facilitates the unique retinal accumulation of LUT and ZEA in humans [22].

Although the functions of macular xanthophylls as preventers of AMD are promising, links between LUT and ZEA and diabetic retinopathy and other degenerative eye diseases are less established. Future investigations should consider the mechanisms of transport and regulation of LUT and ZEA in the retina, the non-xanthophyll role of human BCO2, as well as identifying the function of these potentially biologically important apo-carotenoid metabolites.

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