Narrative Review

Potential roles of dietary zeaxanthin and lutein in macular health and function

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Lutein, zeaxanthin, and meso-zeaxanthin are three xanthophyll carotenoid pigments that selectively concentrate in the center of the retina. Humans cannot synthesize lutein and zeaxanthin, so these compounds must be obtained from the diet or supplements, with meso-zeaxanthin being converted from lutein in the macula. Xanthophylls are major components of macular pigments that protect the retina through the provision of oxidant defense and filtering of blue light. The accumulation of these three xanthophylls in the central macula can be quantified with noninvasive methods, such as macular pigment optical density (MPOD). MPOD serves as a useful tool for assessing risk for, and progression of, age-related macular degeneration, the third leading cause of blindness worldwide. Dietary surveys suggest that the dietary intakes of lutein and zeaxanthin are decreasing. In addition to low dietary intake, pregnancy and lactation may compromise the lutein and zeaxanthin status of both the mother and infant. Lutein is found in modest amounts in some orange- and yellow-colored vegetables, yellow corn products, and in egg yolks, but rich sources of zeaxanthin are not commonly consumed. Goji berries contain the highest known levels of zeaxanthin of any food, and regular intake of these bright red berries may help protect against the development of age-related macular degeneration through an increase in MPOD. The purpose of this review is to summarize the protective function of macular xanthophylls in the eye, speculate on the compounds' role in maternal and infant health, suggest the establishment of recommended dietary values for lutein and zeaxanthin, and introduce goji berries as a rich food source of zeaxanthin.

INTRODUCTION

Epidemiological studies suggest that diets rich in carotenoids can be beneficial for vision, heart, bone health, cognitive performance, and cancer prevention.[1] The current review focuses on the potential role of the xanthophyll carotenoids lutein (L) and zeaxanthin (Z) in eye health, specifically their potential role in reducing the risk of age-related macular degeneration (AMD). A review of the absorption, distribution, and metabolism of L and Z is included, and the current dietary recommendations for these carotenoids, followed by a

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speculation about their putative role in maternal and infant health. The potential value of goji berries as a food with the highest known amount of Z is also presented.

Carotenoids contribute to the bright red, orange, and yellow color in plants.[2] These fat-soluble phytochemicals are classified into 2 categories: carotenes (which include only hydrocarbons) and xanthophylls (eg, L and Z, which also contain oxygen).[3,4] While some dietary carotenoids serve as vitamin A precursors (eg, β-carotene, α-carotene, γ-carotene, and β-cryptoxanthin),[5,6] most of the approximately 100 carotenoids found in plants do not.[7] Among the carotenoids devoid of vitamin A activity are L and Z, along with meso-zeaxanthin (meso-Z), a stereoisomeric metabolite of L.[8]

AGE-RELATED MACULAR DEGENERATION

AMD is the third leading cause of blindness worldwide, after uncorrected refractive errors and cataracts.[9] An estimated 288 million people worldwide are projected to suffer from AMD by 2040.[10] In the United States, the prevalence of early-stage AMD was 9.1 million in 2010, and this number is projected to increase to 17.8 million by 2050.[11] AMD is characterized by a gradual loss of eyesight from the central visual field.[12] Although the exact etiology of AMD is not clear, common pathologic progress includes oxidative stress, lipofuscin toxicity, lipid accumulation, immune dysregulation, and choroidal hyperperfusion.[13] Age-related processes such as a decrease in retinal neuronal elements, alterations in the size and shape of retinal pigmented epithelial (RPE) cells, and thickening of Bruch's membrane further participate in the pathology of AMD.[14] Damage to mitochondria in RPE cells has also been suggested to play a role.[15] Dry AMD, also termed non-exudative AMD, involves the formation of drusen, which are mainly lipid and protein deposits that accumulate between the RPE and Bruch's membrane in the macula.[16] In contrast, wet AMD, also termed exudative or neovascular AMD, is a consequence of abnormal blood vessel formation arising from the choroid, known as choroidal neovascularization (CNV).[17] Clinically, AMD is classified as early- or intermediate-stage based on the size and number of drusen, as well as on the presence of pigmentary changes.[18] AMD is considered late- or advanced-stage in the presence of CNV, where fluid accumulation may result in damage to the neurosensory retina and fibrous scarring, or geographic atrophy (GA), respectively, where loss of the RPE results in damage to overlying photoreceptors and underlying choriocapillaris, causing irreversible vision loss.[19]

The main risk factors for AMD are aging and smoking.[20] Other risk factors may include race, obesity, previous cataract surgery, presence of cardiovascular disease, and hypertension.[21,22] According to the U.S. National Institutes of Health National Eye Institute, the prevalence of AMD is highest among Caucasians, as compared with other races, and higher in females (65%) than in males (35%).[23] Genetic factors are also associated with AMD,[24] with several high-risk single-nucleotide polymorphisms identified from genome-wide association studies.[25–27] The strongest risk variants include the Y402H variant of complement factor H gene, as well as those in the age-related maculopathy susceptibility 2 (*ARMS2*) locus.[28–30] Whether the color of the iris or sunlight exposure are related to the risk of AMD is still being explored.[21,31–35]

Diet may also play a role in the risk of developing AMD. Longitudinal studies have reported that a high intake of fruits and vegetables is associated with a lower risk of AMD.[36,37] Sub-analyses of the age-related eye disease study (AREDS) and AREDS2 trials reported that the dietary intake of selected vitamins, minerals, omega-3 fatty acids, L, and Z, is inversely associated with the risk of progression to late AMD, GA, and large drusen.[38] Similarly, a meta-analysis of 6 longitudinal cohort studies found that the dietary intake of L and Z significantly reduced the risk of GA by 26% and CNV by 32%, with no apparent impact on early stages.[39] A systematic review concluded that adherence to dietary patterns that are high in vegetables, fruits, whole grains, and seafood is associated with a deceased risk for AMD, while diets high in red and processed meats and alcohol may increase the risk.[40]

DIETARY L AND Z

Consuming a diet rich in green leafy vegetables and fish is recommended by the National Eye Institute, for the high carotenoid and omega-3 fatty acid contents.[41] Since humans cannot synthesize carotenoids, these compounds, including L and Z, must also be obtained from the intake of certain fruits, vegetables, corn and corn products, egg yolks, and dairy foods. Commonly consumed foods rich in L (μg/g dry matter) include parsley (64–106), spinach (59–79), and kale (48–115).[42] Leeks (37), peas (19), lettuce (10–48), green pepper (19), red pepper (2.5–85), and pistachios (8–49) are also good sources. Commonly consumed foods rich in Z (μg/g dry matter) are corn tortillas (105) and corn chips (93),[42] as well as cooked egg yolk (5.9) and orange pepper (16.7).[43] Though not commonly consumed, goji berries contain Z in an amount greater than almost any other food. One analysis found the amount of Z (μg/g dry matter) was 1155,[44] while another study noted the Z content ranged from 2800 μg/g dry matter to 5400 μg/g dry matter.[45]

The US intake of L and Z has been decreasing. According to the U.S. National Health and Nutrition Examination Survey (NHANES), the average intakes of L plus Z were 2.15 mg/d in males and 2.21 mg/d in females in 1987, and 2.15 mg/d in males and 1.86 mg/d in females in 1992.[46] In NHANES 2013–2014, the average intakes of L and Z in males and females was 1.58 mg/d and 1.76 mg/d, respectively.[47] Moreover, based on data from NHANES 2003–2004, the reported intake of L was significantly higher than Z in all age groups and ethnicities. However, due to analytical challenges in assessing dietary L and Z separately, most studies present the values together.[48] Since the amount of L in most foods is significantly greater than Z, limited emphasis has been given to the separate roles of Z and L in the macula and potentially other physiological functions.

Goji berries: a rich source of zeaxanthin

Goji berry (*Lycium barbarum* and its closely related species, *Lycium chinense*), also known as wolfberry or Gou Qi Zi, is a rich dietary source of Z. The bright orange-red–colored oval fruit has been used for millennia in traditional Chinese medicine (TCM) for its role in brain, visual, and immune health, its anti-inflammatory benefits, and to help regulate liver and kidney meridians (Figure 1).[44,49,50] Commercially available goji berries and their products come primarily from the Ningxia and Xinjiang autonomous regions in western China,[51] although the hardy, drought-tolerant deciduous shrub can be grown most places in the world in USDA hardiness zones 5–9 (low temperatures from –28.9°F to 30°F; –23.3°C to –1.1°C). Cultivation of goji berries exists in other parts of China, as well as in Japan, Korea, and Taiwan. The Castelli Romani region of Italy (near Rome) cultivates the berries, and they are commercially available for home gardeners in the United Kingdom and the United States, among other locations.

As noted above, goji berries are one of the highest dietary sources of Z.[52,53] The carotenoids are present in both saponifiable and nonsaponifiable fractions of the berry. Additionally, other bioactive compounds found in goji berries include *Lycium barbarum* polysaccharides (LBP), flavonoids, vitamins, minerals, betaine, cerebrosides, phenolic acids, and certain amino acids, which may also support the overall health of the eye, particularly when functioning synergistically.[44,51,54] Although the TCM use of goji berry also includes the leaves and bark of the plant, this review will discuss the potential benefits only from the fruit (fructus lycii) on eye health.

In addition to a robust amount of Z, goji berries contain modest amounts of L, β-cryptoxanthin, β-carotene, and neoxanthin.[49,52,55] The Z and L content among different varieties of dried goji berries cultivated in Ningxia province ranged from 25 mg/100 g to 152 mg/100 g, and 0.3 mg/100 g to 1.9 mg/100 g, respectively.[55] According to the United States Department of Agriculture food database, one serving of goji berries is 28 g, which would provide up to 42.6 mg of L + Z, depending on the cultivar.[56] Moreover, the predominant form of Z in goji berries is a dipalmitate ester linkage.[45] The ratio of Z dipalmitate to total carotenoids was up to 55% and 88%, in fresh and dried goji berry fruit, respectively.[45,57] This esterified form of Z showed a significantly higher intestinal absorption in a caco-2 human intestinal cell model compared with a free Z monoester due to the high efficacy of ester hydrolysis, mainly by carboxyl ester lipase.[58] The high bioavailability of Z from goji berries has also been demonstrated in humans. Plasma Z was significantly increased in individuals consuming 15 g goji berries daily for 28 days, compared with those following a habitual diet.[59] Participants consuming 5 mg of Z dipalmitate extracted from goji berries also showed a higher plasma Z concentration than when they consumed the same amount as unesterified Z over a 9-hour to 24-hour period.[60]

Absorption, distribution, metabolism, and excretion

Among the carotenoids, L and Z are unique in their ability to cross the human blood–retina barrier for accumulation into the macula.[61] After xanthophylls are released from the food matrix by mechanical mixing, digestive enzymes, and gastric acids, these carotenoids follow an absorption path similar to that of other lipids.[61–63] As noted above, esterified forms of xanthophylls appear to be more bioavailable, yet are efficiently hydrolyzed prior to chylomicron insertion by pancreatic cholesterol ester hydrolase or other lipases at the brush border level or within the enterocyte.[64,65] After the transfer from lipid emulsions to intestinal mixed micelles,[63,65] intestinal absorption is thought to occur via both facilitated transport and passive diffusion.[66] Facilitated transport involves enterocyte uptake by CD36, scavenger receptor class B type I, and Niemann-Pick C1-like transporter 1 at the apical membrane.[64] Carotenoids with pro-vitamin A activity undergo cleavage by β-carotene-15′,15′-monoxygenase (BCO1) and β-carotene-9′,10′-dioxygenase (BCO_2) in the intestinal mucosal cells.[67] However, xanthophylls do not undergo cleavage and are packaged directly within chylomicrons.[62,63] The chylomicrons are transported to the liver via the lymph, where they are repackaged into lipoproteins for tissue transport.[62]

The distribution of L and Z across lipoprotein fractions in plasma has been documented. While 80%–85% of carotenoids, including α- and β-carotene and

Figure 1 **Dried goji berries.**

lycopene, are associated with low-density lipoprotein (LDL) particles, 13%–18% are associated with high-density lipoprotein (HDL) particles, and less than 4% are associated with very low density lipoprotein (VLDL) and intermediate-density lipoprotein (IDL).[68] Therefore, some have suggested that L and Z transport into the retina may be dependent on the serum lipid profile.[67,69] A number of studies suggest that HDL dysregulation increases the risk for AMD.[70–72] Some evidence also suggests that macular pigment optical density (MPOD) is inversely associated with the percentage of body fat, after adjusting for age and dietary intake.[69] HDL particles have been shown to be the primary transport mechanism for Z, less so for L, into the retinal pigment epithelium using an ApoA-I knockout mouse model.[73] In humans consuming eggs enriched with L and Z, the L from HDL particles was positively correlated with MPOD.[74] In contrast, other studies have shown that LDL particles are the primary transport vehicles for L and β-carotene, whereas HDL particles are more effective at transporting Z.[65] Lipoprotein particles exchange materials via a variety of transfer proteins (eg, cholesteryl ester transfer protein, phospholipid transfer protein), and some evidence exists that these exchange activities in plasma and interstitial fluid regulate the distribution of carotenoids as well as L and Z across the lipoprotein fractions.[75] However, the exact mechanisms for carotenoid binding to lipoproteins has not been identified.[62] Genetic polymorphisms in key lipoprotein metabolic proteins (eg, lipoprotein lipase, ATP-binding cassette transporter G5) have also been linked with alterations in L and Z concentrations in the retina and with risk of AMD.[76,77] Although the literature on excretion mechanisms is incomplete, some evidence exists that, as expected for lipophilic substances, L and Z are excreted via bile.[78]

Interestingly, in premenopausal women, as much as 34% of L + Z is associated with HDL particles, with enrichment specifically in the HDL2 fraction, which consists of larger HDL particles. Hormonal fluctuations associated with the menstrual cycle are linked with changes in the concentrations of L and Z, with higher xanthophyll content in both LDL and HDL2 in the late follicular phase, when estrogen concentrations are higher than in the luteal phase.

MACULAR PIGMENTS

Lutein, Z, and meso-Z impart a distinctive yellow color to the fovea of primates, the specialized central area of the macular region of the retina rich in cone photoreceptors and optimized for high-acuity central color vision. The compounds have a maximal absorbance at a wavelength near 460 nm and are most concentrated in the inner and outer plexiform layers, which consist primarily of axonal connections between the retinal layers. Lutein and Z are mainly localized in the membranes of photoreceptor axons in Henle's nerve fiber layers and in their outer segments, and are transported into the retina by different binding proteins, including the steroidogenic acute regulatory domain 3 (StARD3) protein (which binds L) and the GSTP1 (which appears to bind Z in the macula of the retina).[62,79,80] Tubulins are abundant in Henle's fibers and also appear to bind carotenoids with high affinity.[81] In primates, the *BCO_2* gene has been reported to be enzymatically inactive, which partially explains some, if not all, of the accumulation of macular xanthophylls in human retinal tissues.[82,83] The accumulation of macular xanthophylls in the tissues and macula of *BCO_2*-knockout mice fed with L and Z further confirms this finding.[84]

The combined density of L and Z is greatest in the center of the macula and decreases with increasing retinal eccentricity.[85,86] In the central fovea, the concentration of Z and meso-Z is higher than that of L at a ratio of 2.4:1. Lutein is most abundant in the peripheral macula, with a Z + meso-Z to L ratio of 1:2 when measured by high-performance liquid chromatography.[87] More specifically, these authors reported the mean L + Z content from 6 adult donor eyes to range from 13.3 ng/mm when assessing the range of 0–0.25 mm from the fovea, 5.7 ng/mm in the range of 0–0.75 mm from the fovea, 2.9 ng/mm at a distance of 0.75–1.6 mm from the fovea, and 0.81 ng/mm and decreasing concentrations when determined at 1.6–2.5 mm from the fovea. Newer data obtained by confocal resonance Raman microscopy suggests that the Z+meso-Z to L ratio is as high as 9:1 at the central fovea.[88] The concentration of L and Z in different parts of the macula appear driven by the spatial constriction of their binding proteins.[62] Interestingly, although

the retina is considered an extension of the central nervous system, the relative concentration of L and Z in the retina compared with the brain is nearly 40-fold higher in the retina, suggesting specific mechanisms of xanthophyll transport.[89,90]

Protection from blue light is critical for eye health. Compared with longer wavelengths of visible light, short blue wavelengths are higher in energy and generate reactive oxygen species (ROS).[91,92] Zeaxanthin can provide stronger oxidant defense than L during photooxidation,[93] while lutein has a greater capacity to absorb short-wavelength light irradiation in lipid membranes.[94] Compared with other carotenoids (eg, lycopene or β-carotene), L and Z are more effective in scavenging ROS and can also reduce phospholipid peroxidation.[95,96] The RPE complex in the outer retina is particularly susceptible to ROS damage due to its high polyunsaturated lipid content (Figure 2).[97] Quenching of singlet oxygen appeared best when L, Z, and meso-Z were mixed in equal ratios rather than separately, when assessed in an eye tissue model, suggesting some synergy between the these macular pigments in their antioxidant properties.[98]

The most common method for quantifying xanthophylls in the retina is assessment of MPOD. This parameter is measured through techniques such as heterochromatic flicker photometry (HFP), a non-invasive psychophysical technique,[99] fundus reflectometry, resonance Raman spectroscopy, or autofluorescence imaging.[100] The MPOD index is associated with the plasma levels of L and Z,[101–103] and has been used to assess the risk for AMD.[104] Some studies report no significant correlation between MPOD and the risk of AMD,[105] which suggests that other ocular measures may also be useful for obtaining a more complete profile of AMD risk. In human donor eyes, the amount of L and Z was inversely associated with AMD.[106] Supplementation of L, Z, and meso-Z have been shown to significantly increase MPOD in both healthy individuals and patients diagnosed with AMD.[41,107] However, a recent narrative review of 10 studies using foods rich in L and Z has produced inconsistent results, which may be due to the relatively modest amounts of these carotenoids, particularly Z, in foods compared with supplements.[108] Indeed, a number of limitations among the studies was noted, including the different amounts of L and Z ingested or administered, variable duration of interventions, and lack of information about the background diet of the study participants. Importantly, the plasma concentrations of L and Z have been more strongly associated with MPOD than the correlation between MPOD and dietary intake.[109]

Results from dietary interventions

Dietary interventions using L- and Z-rich foods have generated inconsistent results regarding the risk of AMD.[110,111] In a cohort study that assessed dietary carotenoid consumption among individuals without AMD at baseline over more than 20 years, increased predicted plasma carotenoid score of L, Z, β-carotene, α-carotene, and β-cryptoxanthin were associated with a lower risk of advanced, but of not early or intermediate AMD.[112] Another meta-analysis concluded that supplementation with L, Z, and meso-Z significantly increased MPOD levels in both AMD patients and healthy individuals in a dose–response manner.[113]

The AREDS intervention was a multi-center study that assessed the efficacy of dietary antioxidant supplements on subjects who were 50 years to 80 years old, with and without AMD or cataracts, for more than 7 years.[114] The initial study used a formula containing 15 mg of β-carotene, 500 mg of vitamin C, 400 IU of vitamin E, with or without 80 mg of zinc and 2 mg of copper. Lutein and Z were not included, because the scientific evidence

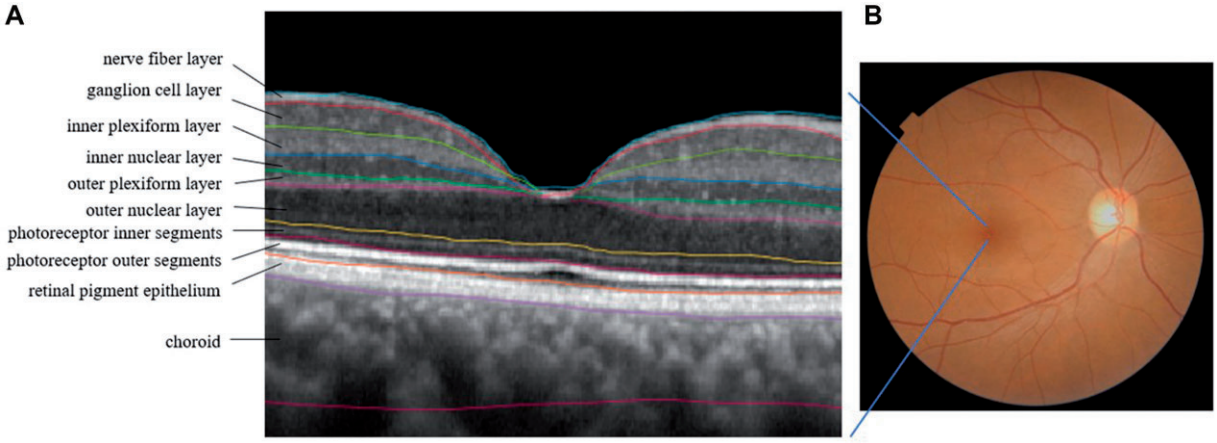

Figure 2 **A. Spectral domain–optical coherence tomography of a macular region, showing anatomical layers. B. Fundus image of a healthy adult retina.** The dark area is the macula; the light area is the optic nerve.

suggesting inclusion these two carotenoids was not yet clear. Compared with the placebo group, participants consuming the antioxidants plus zinc and copper showed a 28% reduction in progression to advanced AMD after 5 years.[115] Subsequently, the AREDS2 was conducted with a newer formulation that included vitamins C and E, either 10 mg of L plus 2 mg of Z, and either 350 mg of docosahexaenoic acid (DHA) plus 650 mg of eicosapentaenoic acid (EPA), or both. Patients were also given either 25 mg or 80 mg of zinc, each with 2 mg of copper. Beta-carotene was eliminated from the supplement due to a potential increased risk of lung cancer among smokers, who were already at high risk for AMD.[116] Primary analyses of the AREDS2 data found no additional benefit in reducing progression to advanced AMD, in comparison with the original AREDS formula. However, in a secondary analysis of combined data from AREDS and AREDS2, the progression risk in those receiving L and Z was significantly lower than in other groups.[117] A recent analysis of the AREDS2 dataset assessing the 10-year risk of developing late AMD evaluated the results from 3882 participants with an average age at baseline of 72 years.[118] Comparisons were made between participants who consumed the initial formula devoid of L and Z, but instead included beta-carotene, with those who consumed the second AREDS formula, where L and Z were included in place of beta-carotene. The hazard ratio for progression to late AMD was 0.91 when comparing those who consumed the second formula containing L and Z with participants who consumed the initial formula devoid of L and Z. Neither of the AREDS clinical trials monitored the MPOD status. To date, the AREDS2 formula remains the standard of care for management of patients with intermediate AMD.

A recent post hoc analysis of a subset of individuals in the AREDS2 study examined the adherence to a Mediterranean diet and the rate of GA enlargement using annual color fundus photographs.[119] Enlargement of GA over a 3.1-year follow-up was significantly slower among those in the highest quartile for dietary intake of whole fruit, alcohol, and the ratio of monounsaturated : polyunsaturated fatty acids, while the rate was faster among participants with the highest red meat intake. The dietary survey data did not distinguish which fruits were associated with the favorable outcomes, but estimated that 14 medium size servings per week qualified for the highest quartile. The association between red meat intake and rate of enlargement of GA is consistent with a systemic review reporting this pattern to be associated with an increased risk of AMD.[40] However, the observation that moderate alcohol intake was associated with a lower rate of GA enlargement contrasts with a previous systemic review that noted an increased risk of AMD with alcohol intake. The authors conclude that a Mediterranean diet pattern appears to be strongly associated with reduced disease progression across a wide range of AMD diseases. Such a diet is rich in colorful fruits and vegetables abundant in carotenoids, including L and Z.[120] More attention to dietary factors that can address the rising incidence of AMD is warranted.

The high Z content of goji berries has led to them being proposed as a dietary source to reduce the risk of AMD, although studies are limited.[63] In one study, circulating Z levels were significantly higher in healthy older individuals who consumed 10 mg of Z extract from goji berries daily for 90 days.[121] No change in macular pigmentation or small drusen was observed, but MPOD was not measured. In an uncontrolled trial, individuals with early-stage AMD who consumed a beverage containing 12 mg of L and 2 mg of Z derived from marigold flower and goji berry, respectively, daily for 5 months, showed higher circulating levels of L and Z, lower intraocular pressures, and better best-corrected visual acuity (BCVA) scores.[122] Unfortunately, the study lacked a control group, and did not clarify whether the form of Z extracted from goji berry was the dipalmitate ester. Another study investigating the effects of a herbal formula among healthy adults with dry eyes noted that chewable tablets providing L (6 mg, 10 mg, or 14 mg) and Z (1.2 mg, 2.2 mg, or 2.8 mg) from extracts of blackcurrant, chrysanthemum, and goji berry showed dose-dependent reductions in eye fatigue symptoms, and tear secretion, as well as improved MPOD, compared with the placebo.[123] The basis of this formula was derived from TCM, so the multicomponent formulation could not directly inform the role of any single ingredient. A study in patients with early AMD reported that the MPOD was significantly higher in those consuming 25 g/day of goji berries (containing approximately 15 mg of Z and 2.5 mg of L) for 90 days, compared with their baseline levels and with a habitual diet control group. The BCVA was also significantly improved in the goji berry group compared with their baseline values.[124] The MPOD and skin carotenoid scores were recently reported to be significantly increased in healthy middle-aged individuals consuming 28 g/day of goji berries (containing approximately 28.8 mg of Z and an estimated 0.15 mg of L) 5 times a day for 90 days, compared with a group taking a supplement with 6 mg of L and 4 mg of Z.[125] These results illustrate that MPOD levels can increase in healthy individuals, even without early signs of AMD. While these results are encouraging, longer intervention periods with a larger number of participants are necessary for a more complete understanding.

In addition to AMD, goji berries have been studied as a therapy for retinitis pigmentosa, an inherited

retinal disease. Patients who consume 0.35 g/d of LBP for 12 months showed a significant improvement in visual acuity and macular thickness, compared with control subjects who did not consume L or Z.[126] Examples of human studies that evaluated the effects of supplements containing goji berries on retinal health are shown in Table 1.[121–126]

Based on preclinical evidence, potential benefits from goji berries on glaucoma and diabetic retinopathy may also exist. Goji berry extract ameliorated the high glucose–induced blood–retinal barrier disruption in human retinal pigment epithelial cells.[127] Studies further reported that LBP showed significant neuroprotective effects over retinal ganglion cells in male C57BL/6N mice and Sprague-Dawley rats with ocular hypertension.[128–130] In db/db mice, goji berry extract restored the thickness of the retina, the ganglion cell number, and the integrity of RPE after daily intake over 8 weeks.[131]

Although research on the upper limit of goji berry intake is scarce, goji berry allergy risk has been associated with the existence of cross-reactivity to nonspecific lipid transfer proteins from peaches, tomatoes, tobacco, tree nuts, and select pollens.[132,133] In addition, bleeding symptoms after consuming goji berry juice, tea, or wine have been described in case reports among patients taking warfarin, an anticoagulant medicine.[134,135]

INFANT MACULAR DEVELOPMENT AND MATERNAL AMD RISK

The average dietary consumption of L and Z among females in the United States is estimated to be 1.76 mg/d, which is substantially below a range of 5 mg/d to 20 mg/d estimated from a recent meta-analysis as being the amount needed to significantly improve MPOD levels among adults with healthy eyes.[107] Therefore, increased maternal intakes of L and Z either through diet or supplementation for the duration of pregnancy and lactation may be of value in the support of fetal and infant eye health.

During development, L and Z are not interchangeable. In a study of 30 mother–infant pairs, serum Z in the newborns and in their mothers was strongly correlated with the MPOD of the babies, but no relationship was noted for either maternal or infant levels of L.[136] The highest plasma levels of maternal Z and L at delivery were associated with a 38% and 32%, respectively, lower risk of visual acuity problems in children at 3 years of age.[137]

The accumulation of L and Z in the macula starts in utero in primates and plays a critical role in visual development and maturation later in life.[138] L and Z were detected from as early as 20 weeks of gestation in macular tissue from human fetuses inspected at autopsy.[87] Unlike in fully matured human eyes, L is the dominant macular pigment in infants under the age of 2 years, regardless of eccentricities. The retina is less mature at birth compared with other eye structures, with complete differentiation requiring 4 years to 5 years.[139] The maturation of the macula is associated with a change in the L:Z ratio over the first 4 years of life, which correlates with the development of cone photoreceptors.[140]

L and Z may also protect against oxidative damage in premature infants, especially those with retinopathy of prematurity (ROP).[141] Premature infants with ROP usually have poor visual acuity, even after laser treatment or intravitreal injection of anti-vascular endothelial growth factor (anti-VEGF) agents.[142] In a model of oxygen-induced retinopathy, mouse pups given L showed less vessel leakage and a lower avascular area compared with those given a L-free control.[143] The authors suggested that the anti-oxidant properties of L may have contributed to these results, although ROS levels were not measured. Studies that investigate L and Z supplementation in ROP babies have produced inconsistent results. In a multi-center, double-blind, randomized controlled trial of very-low-birth-weight infants, no difference was found in the incidence of ROP between those supplemented with daily oral L and Z (0.14 mg L plus 0.6 μg Z) or placebo.[144] However, the progression rate of threshold ROP showed a lower trend in the supplemented group. No adverse events were noted with L and Z supplementation, suggesting that they were well tolerated. Another study examining the effects of daily oral L (0.5 mg/kg) and Z (0.02 mg/kg) supplementation in preterm infants from the seventh day after birth until 40 weeks of age or until hospital discharge found no change in the rate or severity of ROP compared with placebo.[145] Further, a meta-analysis of 3 randomized controlled trials also found no protective association between L and Z supplementation and the risk of ROP.[146]

Human breast milk and infant formula

The L and Z in human milk is particularly important for infant eye and brain development, and may provide long-term benefits to vision and cognition.[147] During gestation, maternal lipoprotein synthesis increases, which accelerates the transport of carotenoids to the fetus.[148] This transfer may deplete maternal stores if the dietary intake of carotenoids in general, and L and Z specifically, is inadequate for maintaining body stores. Low maternal skin and serum carotenoid levels have been reported in mothers of newborn infants.[136]

Table 1 **Human studies on the effects of consumption of goji berries (directly or in supplements) on eye health**

Reference	Sample	Intervention	Frequency and duration	Outcome measures	Results
Bucheli et al. (2011)[121]	150 healthy seniors (aged 65–70 y)	13.7 g/d of a milk-based formulation with 10 mg Z and 68.5 mg vitamin C derived from goji berry OR placebo	Daily for 90 d	Funduscopic exams	The placebo group showed increased hypopigmentation and soft drusen accumulation in the macula, while the treatment group remained stable
Chan et al. (2019)[126]	42 patients with retinitis pigmentosa (aged 26–69 y)	Goji berry OR placebo granules	Daily for 12 mo	Visual acuity, Ganzfeld full-field electroretinogram, Humphrey Visual Field Analysis, and Spectral-domain Optical Coherent Tomography	The treatment group maintained contrast visual acuity and macular thickness, while the placebo group showed a decline in all measures
Kan et al. (2020)[123]	303 healthy individuals with dry eye symptoms (aged 18–65 y)	Three treatment arms giving chewable tablets with the highest L of 14 mg, Z of 2.8 mg, goji berry extract of 175 mg, chrysanthemum extract of 175 mg, and blackcurrant extract of 233 mg, OR placebo	Daily for 90 d	Eye fatigue symptom score, MPOD, Schirmer test, optical coherence tomography, and keratography	The treatment groups showed significantly reduced eye soreness, blurred vision, dry eye, foreign body sensation, and tearing; improved tear secretion and increased first tear break-up time, average tear break-up time, tear meniscus height, and MPOD, compared with the placebo group
Li et al. (2018)[124]	114 patients with early AMD (aged 51–92 y)	25 g/d of dried goji berry OR habitual diet	Daily for 90 d	MPOD, serum L + Z, BCVA	Increased serum Z and MPOD in the goji berry group compared with their baseline levels or with those of the control group
Li et al. (2021)[125]	27 healthy individuals (aged 45–65 y)	28 g/d of dried goji berry OR supplement with 6 mg L and 4 mg Z	Five times a week for 90 d	MPOD, skin carotenoids	Increased MPOD and skin carotenoid score in the goji berry group compared with no significant changes in the supplement group
Peng et al. (2016)[122]	56 patients with early AMD (aged 35–50 y)	60 mL/d of beverage containing 12 mg of L from marigold flower and 2 mg of Z from goji berry	Daily for 5 mo	Serum L and Z, plasma oxidative indices, antioxidant enzymes in erythrocytes, anti-inflammatory markers, BCVA, intraocular pressure, photostress recovery, ocular comfort index, MPOD	The treatment group showed significantly increased serum L and Z, antioxidant capacity, antioxidant enzymes, ocular comfort index, and MPOD; and decreased oxidative stress index, inflammatory markers, BCVA, and interocular pressure compared with baseline values

Abbreviations: AMD, age-related macular degeneration; BCVA, best-corrected visual acuity; L, lutein; MPOD, macular pigment optical density; Z, zeaxanthin.

The concentration of β-carotene, lycopene, L, and Z, the main carotenoids in breast milk, are associated with maternal dietary intake over the first 6 months of lactation.[149] Daily maternal supplementation of either 6 mg of L with 96 µg of Z, or 12 mg of L with 192 µg of Z, over 6 weeks resulted in a dose-dependent increase in L and Z levels in maternal breast milk and plasma, as well as infant plasma levels 3 months to 4 months postpartum.[150] Another study reported that more carotenes were present than xanthophylls in maternal plasma, whereas more xanthophylls than carotenes were presented in breast milk.[151] While more than 1 study is needed to clarify these dynamics, these preliminary findings suggest that maternal–infant transfer of carotenoids may occur, possibly at the expense of the mother. Future studies are needed to clarify whether breastfeeding or L and Z intake may impact their AMD risk.

Studies in premature infants illustrate the importance of L and Z in visual development.[152] In preterm human neonates, extremely low levels of serum L and Z are associated with an undetectable MPOD.[153] When a carotenoid-fortified formula containing 211 µg/L of combined L and Z was given to preterm infants, plasma carotenoid levels became comparable with those of breastfed preterm infants, and were significantly higher than those fed formulas without L or Z fortification.[154] In a small study that monitored the concentration of L and Z in various infant formulas and breastmilk from different mothers, Z was not detected in any formula but was present in all breast milk samples, while L was consistently higher in breast milk.[155] Serum L was also noted to be 6-fold higher in breastfed infants compared with those fed with a formula devoid of L.[156] Further studies are warranted to assess the prospective effects of L- and Z-fortified formula on MPOD and visual development in infants as they enter adulthood.

The L-ZIP supplementation trial is currently exploring whether prenatal supplementation of 10 mg of L and 2 mg of Z will maintain maternal body stores, prevent potential macular pigment depletion during pregnancy, or enhance systemic and ocular carotenoid stores for both mothers and infants.[157] Clinical trials on the long-term effects of perinatal L and Z intake on MPOD changes among mothers and infants are also warranted.[158]

Unfortunately, longitudinal studies on AMD in females often do not include breastfeeding history. A useful study design would be to investigate MPOD levels and relative risks of AMD between multiparous and nulliparous women, and in mothers practicing breastfeeding compared with formula feeding. Dietary intake of L and Z would be important to assess. Another challenge in retrospective studies is that breastfeeding history may not be accurate. Therefore, studies on the maternal transfer of L and Z during pregnancy and lactation with MPOD changes in infants and throughout the lifespan could be important but difficult to conduct. Future research should also focus on the measurement of L and Z status and MPOD in mother–infant pairs of twins as well as mother-babies with short birth intervals.

Estrogen exposure

Reproductive hormone status may be a confounding factor when assessing AMD risk. The pathogenesis of AMD involves oxidative stress and immune dysregulation.[14] Estrogen has been shown to reduce oxidative stress and inflammation in RPE cells as well as systemically.[159,160] Lifetime estrogen exposure, affected by factors such as the number of pregnancies, menopause, reproductive period, oral contraceptive use, and hormone replacement therapy, may influence the risk of developing AMD,[161] but the current evidence is inconsistent. Also unknown is whether maternal L and Z intake during pregnancy and lactation can influence AMD risk for both the mother and, longer-term, for the infant. One study reported that postmenopausal hormone use decreased the risk of neovascular AMD but increased the risk of early AMD, while parous women showed a reduced risk of early AMD but not of neovascular AMD.[162] Two nationwide studies from South Korea among postmenopausal women noted that exogenous estrogen exposure was not a protective factor for AMD. A cohort study found that hormone replacement therapy and a longer reproductive period was associated with an increased risk of neovascular AMD.[163] A cross-sectional study showed that oral contraceptive use was associated with an increased risk of late AMD.[164] In addition, a review summarizing the effect of estrogen exposure and the risk of all age-related eye diseases concluded that hormone replacement therapy, or the use of oral contraceptives, could be either positively or negatively associated with the risk of AMD.[161] In contrast, some studies have reported that a longer duration of breastfeeding may be protective against late but not early AMD,[164,165] even when the estrogen level was low during lactation. Unfortunately, none of the studies cited above explored L or Z dietary intake. Future studies on the interaction of different reproductive and estrogen exposure histories and AMD risk are needed, as well as the effect of supplemental L and Z during pregnancy and lactation.

A DIETARY REFERENCE INTAKE FOR L AND Z?

L and Z fulfill many criteria as essential nutrients, including high concentrations in select tissues,

biological plausibility for eye health, depletion outcomes such as vision impairment in primates, and inverse associations with certain diseases.[166] In addition to their role in eye health, L and Z are involved in cognitive function at all stages of life.[167] A randomized controlled trial reported that L and Z supplementation improved neural efficiency and learning performance by increasing the interaction of numerous brain regions in older adults.[168] Other reports have demonstrated an association between increasing L intake or circulating levels and preventing age-related cognitive decline, reducing the risks of certain cancers, coronary heart disease, stroke, and metabolic syndrome, and achieving higher levels of physical activity.[169–171] A systematic review of in vivo, ex vivo, and in vitro studies concluded that L may benefit vascular health by improving endothelial function, reducing inflammation, regulating favorable lipid profiles, and maintaining glucose homeostasis.[172] Systematic reviews summarizing the amount of L needed for cognitive functions and enhancement of gray matter volume estimated that at least 10 mg/d for 12 months could be beneficial.[173,174]

Age and sex are considered when creating dietary reference intake (DRI) values for established nutrients. A similar context may be appropriate for L and Z. Although the current clinical evidence is not completely consistent regarding the association between age and MPOD,[175] a trend has indicated that the values are lower in older compared with younger individuals.[176] Whether the proposed intake of L and Z should be based on the amount that can increase MPOD, reduce AMD risk, benefit visual maturation in newborns, protect cognitive health, or reduce the risk of other diseases requires further consideration. Sex differences in AMD prevalence must also be considered, especially in relation to pregnancy and lactation, as discussed above.

Currently, L and Z are not included in the United States DRI due to inadequate details from food databases, limited large-scale dietary intake studies, and insufficient knowledge regarding their metabolism, biological functions and interindividual variability.[177] A DRI for L has, however, been promoted for a number of years, since the compound satisfies a well-established set of criteria for consideration.[178,179] Recently, a new 4-step framework for recommended intakes of bioactive dietary compounds was advanced that features L and Z as key examples of substances that promote health but are not essential for preventing classic deficiency diseases.[180] As the authors note, knowledge maps may be useful tools to help expand the criteria for a DRI, as well as using enhancement of physiological function (in this case, L and Z for improving MPOD and reducing the risk of AMD). Establishing a DRI for L and Z, either separately or together, would further emphasize the importance of consuming fruits and vegetables rich in a variety of colors, adding more specificity beyond a general recommendation of the number of servings of fruits and vegetables in general. A specific recommendation for L and Z would also provide a benchmark for intake and enable better assessment for determining whether various populations are meeting their needs for visual health.

Dietary supplements

Numerous dietary supplements containing L and Z are available in the United States and worldwide, perhaps due in part to the notation on the US National Institutes of Health, Office of Dietary Supplements website identifying the AREDS2 supplement containing L and Z as one of 4 examples of effective dietary supplements.[181] However, the amount of L and Z, along with other ingredients, varies widely in dietary supplements promoted for eye health, with some replicating the AREDS2 formulation, while others contain both higher amounts of select vitamins and minerals, and additional botanicals.[182] Even with the evidence that the AREDS2 formula may reduce the risk of progression from intermediate to advanced AMD, and the multitude of product claims for products that "promote", "protect", or "support" vision and eye health, no dietary supplements on the market have been shown to help with primary prevention of AMD or other eye diseases, or to reduce the risk of progression from early to intermediate AMD.

The amount of L and Z in foods and dietary supplements appears to be safe.[183] No adverse events were found in clinical trials administering L at 30 mg/d for 120 days or 40 mg/d for 63 days.[184,185] The only reported adverse effect after a daily supplementation of 15 mg L in a 20-week trial was a single case of self-reported carotenodermia, a reversible condition of orange skin color.[186] Although a higher amount has been used in human studies, after assessing the potential risks, the observed upper safety level for L has been proposed as 20 mg/d.[187] The European Food Safety Authority concluded that safe upper limits for L and Z for use in dietary supplements were 1 mg/kg body weight/d and 0.75 mg/kg body weight/d, respectively.[188,189]

In primate models, rhesus monkeys fed a xanthophyll-free diet for 3 years to 6.5 years developed extremely deficient or absent macular yellow pigment and drusen-like bodies.[190] When 2.2 mg/kg (3.9 µmol/kg) per day of L or Z were supplemented for 24 weeks to 101 weeks, the rhesus monkeys showed significant increases in their corresponding serum, retinal, and adipose tissue concentrations.[191] In their retina samples, L

and meso-Z, but not Z, appeared in the L-supplemented group, while only Z was found in the group supplemented with Z. In humans, a study investigating the serum and macular responses of L, Z, and meso-Z from dietary supplements found that 13.13 mg/d for 12 weeks provided maximum MPOD increases, whereas 7.44 mg/d was the amount that increased serum levels with the highest efficacy.[192] These and other studies support the need to consider dietary recommendations for L and Z, particularly as conditionally essential nutrients, due to their protective effects on eye health.[193]

CONCLUSION

Macular xanthophylls cannot be synthesized de novo in primates. The oxidative defense and blue light filtering characteristics of L, Z, and meso-Z are important for visual function and potentially reducing the risk of AMD. Because L and Z storage in the maternal body during pregnancy and lactation may become depleted due to active transfer to the offspring, more attention to safe and robust intake of foods and dietary supplements containing these xanthophylls is warranted. Since many infant formula products are not fortified with L or Z, addition of these two xanthophylls should also be considered.

The impact of foods and dietary supplements rich in L and Z on MPOD and visual function among AMD patients and in healthy individuals deserves further attention. Since Z may play a different role from that of L in terms of macular pigment development or protection, better analytical techniques are needed to reassess food composition databases to distinguish these compounds, with greater attention paid to Z as a standalone food component, rather than grouping it with other xanthophylls. A reexamination of the US DRI status for L and Z is also warranted.

Goji berries have the highest known content of Z of any commonly consumed food, which also comes in a unique dipalmitate ester form. Given the increasing rates of AMD worldwide, goji berries, along with L and Z supplements, may help reduce this escalation.

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