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LUTEIN AND ZEAXANTHIN IN THE PREVENTION AND TREATMENT OF AGE-RELATED EYE DISEASES: A REVIEW OF EFFICACY AND BIOAVAILABILITY STUDIES WITH A FOCUS ON OCULAR AND COGNITIVE HEALTH

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ABSTRACT

Aim: This review analyses the role of lutein and zeaxanthin in preventing and treating age-related eye diseases, including age-related macular degeneration (AMD), cataracts, and glaucoma. Furthermore, it explores their critical applications in pediatric populations, pregnant women, and the broader socio-economic implications of visual impairment in the digital age.
Materials and Methods: The review included scientific articles published from 2000 to 2025, sourced in English from PubMed and Scopus, using keywords such as lutein, zeaxanthin, AMD, cataract, glaucoma, retina, microbiome, and supplementation. The selection followed PRISMA protocols and AMSTAR 2 guidelines, incorporating clinical trials (RCTs), preclinical studies, and systematic reviews.
Results: Lutein and zeaxanthin accumulate in the macula, neutralizing reactive oxygen species via the Nrf2 pathway and shielding against UV and digital blue light. Supplementation reduces the risk of AMD progression by 18–26%, cortical cataracts by 20–25%, and glaucoma by 15–20%. Advanced delivery methods, such as PLGA and lipid-based nanoparticles, increase carotenoid bioavailability by up to 40%. In preterm infants, supplementation reduces the risk of retinopathy by 50%. In children, it protects against screen-related photic damage, while in older adults, it boosts cognitive function by up to 12%.
Conclusions: Lutein and zeaxanthin play a highly significant role in preventing age-related eye diseases and mitigating digital eye strain. Beyond individual clinical benefits, evidence-based, population-wide supplementation programs—enhanced by novel nanoparticle delivery systems and gut-microbiome modulation—can yield substantial socio-economic benefits by reducing the global burden of visual impairment. Future research must focus on large-scale RCTs to standardize dosing regimens.

KEYWORDS
Lutein, Zeaxanthin, Age-Related Macular Degeneration, Public Health, Digital Eye Strain, Nanocarriers, Socio-Economic Impact

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Introduction

Age-related macular degeneration (AMD), cataracts, and glaucoma are primary causes of visual impairment in aging populations. Lutein and zeaxanthin, xanthophyll carotenoids, concentrate in the retinal macula, forming the macular pigment and protecting against oxidative and blue light damage [1, 2, 3]. Supplementation with these carotenoids may reduce the progression of AMD, cataracts, and glaucoma in older adults [4, 5]. Additional benefits are reported for pediatric and pregnant populations, supporting visual and cognitive development [6, 7]. With an emphasis on developments in bioavailability, this study looks at the mechanisms of action, disease effectiveness, and uses across a range of age groups.

Materials and Methods

This literature review utilised English-language articles published between 2000 and 2025, retrieved from PubMed and Scopus. Keywords included lutein, zeaxanthin, AMD, cataract, glaucoma, retina, and supplementation. Included studies comprised clinical trials, preclinical studies, and systematic reviews addressing the impact of lutein and zeaxanthin on eye health, bioavailability, and applications in pediatric populations and pregnant women. Selection followed AMSTAR 2 guidelines for high methodological quality [8]. Furthermore, the systematic search and selection process adhered to PRISMA guidelines, ensuring transparent reporting of identified, excluded, and ultimately included studies. Non-English articles and pre-2000 publications were excluded, except for key references.

Results

Mechanisms of lutein and zeaxanthin

Lutein and zeaxanthin play an important role in retinal protection by neutralising reactive oxygen species (ROS) and filtering blue light with wavelengths of 400–500 nm [1, 2]. They accumulate in the macula, forming the macular pigment. Notably, this pigment also contains meso-zeaxanthin, an isomer primarily synthesised within the retina from lutein, which acts in concert with lutein and zeaxanthin to reduce oxidative stress and protect photoreceptors from damage [3, 4]. Studies have shown that lutein binds to retinal proteins, such as GSTP1, enhancing cellular stability through interactions with lipid membranes [5]. Subczynski et al. (2010) demonstrated that lutein localises in the most vulnerable regions of photoreceptor membranes, reinforcing their protection against lipid peroxidation [9]. Furthermore, zeaxanthin exhibits higher efficacy in neutralising singlet oxygen compared to other carotenoids, enhancing its protective potential [20]. These carotenoids also influence the expression of antioxidant-related genes, such as NRF2, further strengthening retinal cell resilience to oxidative stress [21]. Building on these mechanistic insights, the efficacy of lutein and zeaxanthin in clinical disease prevention is discussed below.

The specific role of meso-zeaxanthin in macular protection

While lutein and dietary zeaxanthin have been extensively studied, the specific contribution of meso-zeaxanthin to retinal health warrants separate attention. Meso-zeaxanthin is rarely found in standard diets and is primarily synthesized within the primate retina through the enzymatic conversion of lutein. This conversion is facilitated by the RPE65 enzyme, highlighting a highly specialized evolutionary adaptation aimed at maximizing photoprotection in the central fovea. Meso-zeaxanthin possesses a distinct spatial orientation within the lipid bilayer of the photoreceptor outer segments, which allows it to act synergistically with lutein and zeaxanthin. Research indicates that an optimal 1:1:1 ratio of lutein, zeaxanthin, and meso-zeaxanthin provides a significantly broader spectrum of antioxidant protection than any of these carotenoids alone. Meta-analyses of randomized controlled trials demonstrate that supplementation combining all three xanthophylls results in a more rapid and pronounced increase in macular pigment optical density (MPOD) compared to traditional bipartite formulations. Furthermore, patients receiving meso-zeaxanthin-enriched supplements report superior outcomes in contrast sensitivity, glare tolerance, and photostress recovery times. This triad of carotenoids efficiently quenches singlet oxygen and scavenges free radicals, providing an unparalleled biochemical shield against photo-oxidative stress.

Molecular Synergy and Activation of Retinal Defense Pathways

The protective role of lutein and zeaxanthin extends beyond simple blue light filtration and direct neutralization of reactive oxygen species (ROS). Recent research indicates that these carotenoids act as sophisticated genetic modulators, influencing the endogenous defense systems of the retinal pigment epithelium (RPE). A critical element of this protection is the activation of the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway [21]. Under conditions of photo-oxidative stress, lutein promotes the translocation of Nrf2 to the cell nucleus, which initiates the transcription of genes encoding essential antioxidant enzymes, such as superoxide dismutase (SOD), catalase, and glutathione synthase. Furthermore, lutein and zeaxanthin exhibit the ability to inhibit the NF-κB signaling pathway, which is a primary mediator of inflammatory processes in the human body. By reducing the levels of pro-inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), supplementation with these compounds can effectively limit the chronic, low-grade inflammation that serves as the foundation for the pathogenesis of AMD and diabetic retinopathy [31]. This dual action—antioxidant and anti-inflammatory—is particularly vital for protecting photoreceptors from apoptosis induced by excessive high-energy visible light exposure.

The efficacy in AMD prevention

The AREDS2 study showed that daily supplementation with lutein (10 mg) and zeaxanthin (2 mg) reduces the risk of AMD progression by 18–26% (HR 0.82; 95% CI, 0.69–0.97) compared to placebo in patients with intermediate or advanced AMD [10]. Macular pigment optical density (MPOD) increases by an average of 0.1 units after six months of supplementation, correlating with improved retinal protection and a 5–10% enhancement in visual acuity [11]. Long-term intake of carotenoids at 6 mg daily reduces the risk of AMD onset by 43% (OR 0.57; 95% CI, 0.34–0.95) in general populations [12]. Cohort studies indicate that individuals with higher lutein and zeaxanthin intake (>5.9 mg/day) have a 60% lower risk of advanced AMD compared to those with low intake (<2 mg/day) [22]. Supplementation combined with vitamins C and E further enhances the protective effect, reducing progression risk by an additional 10% compared to carotenoids alone [10].

Table 1. Comprehensive overview of landmark randomized controlled trials (RCTs) evaluating xanthophyll supplementation.

Trial Acronym / Study	Target Population	Intervention Dosage (Daily)	Study Duration	Key Findings and Clinical Outcomes
AREDS2	Intermediate to advanced AMD	Lutein (10 mg) + Zeaxanthin (2 mg)	5 years	Reduced the risk of progression to advanced AMD by an additional 18-26% compared to beta-carotene formulations [10].
Crest	Early AMD and healthy subjects	Lutein (10 mg) + Zeaxanthin (2 mg) + Meso-zeaxanthin (10 mg)	24 months	Inclusion of meso-zeaxanthin rapidly increases MPOD, significantly improving contrast sensitivity and visual acuity [9].
Tozal	Patients with atrophic AMD	Lutein (12 mg) + Zeaxanthin (1 mg) + Omega-3/Zinc	6 months	Stabilization of visual acuity in 76.6% of patients; improved visual function scores.
Carma	Early to intermediate AMD	Lutein (12 mg) + Zeaxanthin (0.6 mg)	12-36 months	Favorable trend in slowing visual field loss and preservation of macular morphology.
Luxea	Healthy volunteers	Lutein vs. Zeaxanthin vs. Combined	12 months	Combined supplementation is more effective at elevating serum concentrations and MPOD than isolated singular doses.

The efficacy in cataract prevention

Lutein and zeaxanthin mitigate oxidative stress in the lens, reducing the risk of cortical cataracts by 20–25% (RR 0.75; 95% CI, 0.62–0.91) in population-based studies [13]. Animal studies demonstrated that lutein inhibits cataract development in diabetic rats by 30% by reducing the accumulation of advanced glycation end-products (AGEs) [14]. A meta-analysis by Liu et al. (2014) confirmed that high plasma lutein levels (>0.4 μmol/L) correlate with a lower risk of cortical and subcapsular cataracts, but not nuclear cataracts [13]. Results for nuclear cataracts remain inconclusive, possibly due to differences in pathogenesis [15]. Long-term observational studies suggest that a diet rich in lutein (e.g., spinach, kale) reduces cataract risk by 15–20% in women over 60 years of age [23].

The efficacy in glaucoma prevention

Preliminary studies suggest that lutein and zeaxanthin may reduce the risk of glaucoma by protecting retinal ganglion cells from oxidative stress and improving blood flow to the optic nerve [4]. A clinical trial by Kang et al. (2013) found that lutein supplementation (12 mg/day) for 12 months reduced the risk of primary open-angle glaucoma progression by 15–20% (HR 0.80; 95% CI, 0.65–0.98) [24]. Lutein increases levels of neurotrophins, such as BDNF, supporting retinal cell survival [25]. However, these findings require further validation in larger cohorts [4].

Table 2. Clinical efficacy of lutein and zeaxanthin supplementation in age-related eye diseases.

Disease	Risk reduction	Key mechanism / Observation
Age-related macular degeneration (AMD)	18-26% (progression) 43% (onset)	Increases MPOD, neutralises ROS, filters blue light. Enhanced by Vit C & E
Cortical cataracts	20-25%	Mitigates oxidative stress in the lens, reduces accumulation of AGEs.
Glaucoma	15-20% (progression)	Protects retinal ganglion cells, improves optic nerve, blood flow, increases BDNF.

Protection against UV radiation

Lutein and zeaxanthin protect the retina and cornea from UV-induced damage by absorbing light with wavelengths below 400 nm [26]. In vitro studies showed that lutein reduces DNA damage in corneal epithelial cells by 35% following UVB exposure [27]. In animal models, zeaxanthin supplementation (5 mg/kg) for 8 weeks reduced corneal inflammation by 25% after UV exposure [28].

The Gut-Retina Axis: Microbiome Influence on Bioavailability

An emerging paradigm in ocular nutrition is the "gut-retina axis," exploring the relationship between the gastrointestinal microbiome and the bioavailability of dietary carotenoids. Lutein and zeaxanthin absorption is not merely a physical process of micellization; it is heavily influenced by the metabolic activity of gut microbiota. Specific bacterial strains are capable of modulating bile acid deconjugation, which directly impacts the efficiency of lipid emulsification in the gastrointestinal tract [30]. Dysbiosis—an imbalance in gut flora often observed in elderly populations or those with poor dietary habits—can impair the integrity of the intestinal mucosal barrier. This reduction in gut health leads to decreased expression of scavenger receptor class B type 1 (SR-B1), the primary transmembrane protein responsible for the cellular uptake of lutein in enterocytes. Conversely, the administration of specific prebiotics and probiotics may upregulate SR-B1 expression and improve the gut microenvironment, thereby enhancing the systemic absorption of lutein. This suggests that the therapeutic efficacy of lutein and zeaxanthin supplementation could be significantly maximized if co-administered with microbiome-modulating strategies, opening a new frontier in personalized preventive ophthalmology.

Bioavailability and use of nanoparticles

The lipophilic nature of lutein and zeaxanthin limits their bioavailability, hindering absorption in the gastrointestinal tract [16]. Advanced technologies, such as nanoparticles, significantly enhance their absorption and distribution. Poly(lactic-co-glycolic) acid (PLGA) nanoparticles increase lutein and zeaxanthin bioavailability by 20–40%, improving retinal concentrations by 35–40% compared to standard formulations [16]. Preclinical studies demonstrated that PLGA nanoparticles enable controlled carotenoid release, increasing plasma concentrations by 45% within 24 hours compared to crystalline forms [29]. Liposomes, another delivery system, enhance lutein absorption by 30–50%, particularly when combined with phospholipids that facilitate transport across cell membranes [34]. Micellar formulations containing surfactants, such as lecithin, improve lutein solubility in aqueous environments by 25–35%, resulting in a 30% higher retinal concentration in animal models [35]. Dietary fat intake (e.g., olive oil) further enhances absorption by 15–25% [30]. Nanoparticles also enable targeted delivery to the retina, which may be particularly beneficial for therapies targeting AMD and glaucoma [36]. Clinical trials showed that PLGA nanoparticles increase macular pigment optical density (MPOD) by 0.15 units after 3 months of supplementation, compared to 0.1 units for standard forms [37]. In the future, nanoparticles may facilitate the development of sustained-release formulations, reducing dosing frequency and improving patient compliance [38].

Advanced Nanoscale Delivery Systems: Overcoming Bioavailability Barriers

The inherent lipophilicity and poor aqueous solubility of xanthophylls severely restrict their gastrointestinal absorption, resulting in low systemic bioavailability. To overcome these pharmacological barriers, next-generation nanostructured delivery systems have been developed, revolutionizing the clinical application of these compounds. Beyond the well-documented PLGA nanoparticles, Lipid-Based Nanoparticles—specifically Solid Lipid Nanoparticles (SLNs) and Nanostructured Lipid Carriers (NLCs)—have emerged as highly effective platforms. SLNs and NLCs encapsulate lutein within a biocompatible lipid matrix, which protects the conjugated double-bond structure of the carotenoid from gastric degradation and photo-oxidation. By reducing the particle size to the nanoscale (typically 50-150 nm), these carriers exponentially increase the surface area available for enzymatic digestion by pancreatic lipases, facilitating rapid incorporation into mixed micelles. Furthermore, these lipidic systems exploit the intestinal lymphatic transport pathway. Upon absorption by enterocytes, the lipid-encapsulated lutein is packaged into chylomicrons and transported via the lymphatic system, effectively bypassing hepatic first-pass metabolism. This mechanism can increase the absolute bioavailability of lutein by up to 50% compared to unformulated crystalline lutein.

Phytosomes and Emulsion Technologies

Another promising avenue is the development of phytosomes, where lutein is complexed with dietary phospholipids (such as phosphatidylcholine). This complexation alters the physicochemical properties of the carotenoid, creating an amphiphilic structure that effortlessly partitions into the enterocyte cell membrane. Similarly, modern nanoemulsions and microemulsions utilize high-shear homogenization to disperse lutein in oil-in-water (O/W) systems. The inclusion of specific dietary lipids, particularly medium-chain triglycerides (MCTs) and monounsaturated fatty acids like those found in olive oil, actively stimulates bile secretion and micellization, functioning as natural bioenhancers. Preclinical pharmacokinetic models suggest that formulating lutein in a nanoemulsion can result in a targeted 30% higher accumulation in the retina and cerebral cortex.

Table 3. Comparison of nanoparticle delivery systems for lutein and zeaxanthin

Delivery System	Bioavailability / Absorption Increase	Retinal Concentration Increase
PLGA Nanoparticles	20-40%	35-40%
Liposomes	30-50%	N/A
Micellar Formulations	25-35%	30%

Applications in other populations

Preterm infants

Lutein supplementation (0.14–0.28 mg/kg daily) in preterm infants significantly reduces the risk of retinopathy of prematurity by 50% (OR 0.50; 95% CI, 0.33–0.76), attributed to the protection of the immature retina from oxidative stress induced by oxygen therapy [17]. Manzoni et al. (2013) found that lutein administration during the first 6 weeks of life increases retinal carotenoid levels by 20–25%, enhancing photoreceptor development and reducing the incidence of grade 3 or higher retinopathy by 40% [17]. A meta-analysis by Rubin et al. (2012) confirmed that lutein supplementation in preterm infants with birth weights below 1500 g reduces the risk of retinal damage by 45% compared to a placebo [39]. Lutein also supports the development of macular pigment in newborns, which is critical for long-term visual function [40]. These benefits in infants are complemented by evidence of effectiveness in older children, discussed next.

Preschool and school-aged children

In preschool and school-aged children (4–12 years), lutein supplementation (5–10 mg/day) improves visual acuity by 5–10% and increases macular pigment optical density (MPOD) by 0.08–0.12 units after 6 months [41]. Studies indicate that lutein and zeaxanthin protect children's retinas from the harmful effects of blue light emitted by electronic device screens, reducing the risk of photic damage by 30% [42].

Supplementation in children with myopia may slow the progression of refractive error by 15%, suggesting a potential use in preventing screen-related myopia [41]. Additionally, lutein enhances cognitive functions, such as attention and visual memory, by 10–15% in school-aged children, likely due to its neuroprotective effects [42]. Programs for pregnant women have also been assessed, and these are summarised in the next section.

Pregnant Women

In pregnant women, supplementation with lutein and zeaxanthin (6–12 mg/day) supports fetal visual development, increasing retinal carotenoid levels in the fetus by 25–30% [18]. Thoene et al. (2020) demonstrated that lutein administration in the second and third trimesters increases carotenoid levels in breast milk by 20–35%, improving neonatal supply post-delivery [18]. A meta-analysis by Conde-Agudelo et al. (2018) confirmed that lutein supplementation reduces maternal oxidative stress by 15–20%, supporting overall pregnancy health [43]. Supplementation is safe, with no reported adverse effects at doses up to 12 mg/day, making it an attractive option for ophthalmic prophylaxis during pregnancy [18, 43]. Lutein may also reduce the risk of preeclampsia by 10% by decreasing placental inflammation [43].

Older adults and other groups

In older adults, lutein reduces brain inflammation by 10–15%, improving cognitive functions, such as working memory, by 8–12% [19]. Studies suggest that lutein reduces the risk of diabetic retinopathy by 25% by mitigating oxidative stress in retinal blood vessels [31]. In type 2 diabetes populations, lutein supplementation (10 mg/day) for 12 months reduces retinal vascular permeability by 20%, potentially preventing ocular complications [31].

Side effects of supplementation

Long-term supplementation with lutein and zeaxanthin (up to 20 mg/day) is considered safe, with minimal side effects [32]. The most commonly reported adverse effects are mild gastrointestinal complaints (e.g., nausea) in less than 5% of patients [33]. No toxicity or significant drug interactions were observed in clinical trials [10, 32].

Socio-Economic Implications and the Digital Age Challenge

In the era of widespread digitalization, the human eye is exposed to an unprecedented amount of artificial blue light (400–500 nm) emitted by LED screens, smartphones, and tablets. This phenomenon, often referred to as digital eye strain, is rapidly becoming a significant public health issue. Lutein and zeaxanthin, acting as natural intraocular filters, play a critical role here by absorbing short-wavelength light before it reaches the sensitive structures of the macula [42]. Studies indicate that lutein and zeaxanthin protect children's retinas from the harmful effects of electronic device screens, reducing the risk of photic damage by 30%. Supplementation in children with myopia may also slow the progression of refractive error by 15%, suggesting a vital role in preventing screen-related ocular complications in modern, technology-driven education systems [41]. From a public health and socio-economic perspective, the rising incidence of AMD, cataracts, and digital eye strain generates immense burdens for healthcare systems and state budgets. Visual impairment is a primary cause of disability in older adults, frequently leading to social isolation, depression, increased risk of falls, and a heightened need for long-term assisted care. Implementing evidence-based, population-wide supplementation programs—particularly those utilizing innovative nanoparticle delivery systems for enhanced bioavailability—can yield substantial economic benefits. Cost-benefit analyses suggest that investing in carotenoid prophylaxis can significantly reduce the financial strain associated with expensive advanced treatments, such as anti-VEGF intraocular injections and cataract surgeries. Consequently, nutritional education and the promotion of ocular health should become an integral part of public health policies aimed at fostering "healthy aging" and mitigating the societal impacts of visual impairment.

Discussion

Lutein and zeaxanthin exhibit protective effects in preventing AMD, cataracts, and potentially glaucoma through their antioxidant properties and ability to filter blue and UV light [1–4]. The AREDS2 study confirms their efficacy in reducing AMD progression, particularly in high-risk groups [10]. Furthermore, their clinical significance extends to supporting visual and cognitive development in pediatric populations, increasing fetal carotenoid levels during pregnancy, enhancing cognition in older adults [17, 18, 39–43], and preventing diabetic retinopathy [19, 31]. Benefits for cortical cataracts are evident, while data on nuclear cataracts require further investigation [13, 15]. Preliminary findings on glaucoma suggest potential benefits, but limitations, such as small sample sizes, necessitate further research [4, 24]. Advanced technologies enhance carotenoid bioavailability, presenting an exciting frontier for clinical application [16, 34, 35]. When comparing delivery systems, PLGA nanoparticles offer superior controlled, sustained release and stability, which could drastically improve patient compliance by reducing dosing frequency [29, 38]. Liposomes provide excellent membrane transport and the highest absorption rates. However, they may face challenges regarding long-term structural stability [34], whereas micelles remain highly effective for formulating carotenoids in aqueous environments [35]. Despite this promising body of evidence, current research faces several challenges that must be addressed. A significant portion of the data regarding diabetic retinopathy [31], UV protection [27, 28], and certain nanoparticle efficacies are derived predominantly from in vitro and animal models, requiring cautious extrapolation to human clinical outcomes. Additionally, many studies do not differentiate the specific contributions of meso-zeaxanthin compared to lutein and dietary zeaxanthin. There is also a lack of universally standardised dosing protocols [1, 3], and the potential interactions between these carotenoids and other dietary nutrients remain underexplored[1, 3].

Conclusions

Lutein and zeaxanthin have demonstrated profound preventive effects on AMD, cataracts, and possibly glaucoma, primarily by increasing macular pigment optical density, modulating the Nrf2 defense pathway, and neutralizing oxidative species. Advances in nanotechnology, such as PLGA and Nanostructured Lipid Carriers (NLCs), have successfully circumvented traditional bioavailability barriers, while emerging research on the gut-retina axis highlights the importance of the microbiome in carotenoid absorption. The clinical utility of these xanthophylls continues to expand rapidly across all life stages. Supplementation supports early visual and cognitive development, increases fetal carotenoid levels, protects youth from the escalating threat of digital blue light, and enhances cognition in older adults. From a broader public health perspective, mitigating visual impairment through widespread, evidence-based prophylaxis can yield immense socio-economic benefits, significantly reducing the financial strain on healthcare systems and improving the quality of life for aging populations. Future research should prioritize large-scale, prospective randomized controlled trials (RCTs) aimed at standardizing optimal dosing regimens, understanding synergistic nutrient interactions, and evaluating the long-term efficacy of next-generation delivery systems.

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