Phytochemicals and age-related eye diseases

Michael Rhone and Arpita Basu

Cataracts, glaucoma, and age-related macular degeneration (AMD) are common causes of blindness in the elderly population of the United States. Additional risk factors include obesity, smoking, and inadequate antioxidant status. Phytochemicals, as antioxidants and anti-inflammatory agents, may help prevent or delay the progression of these eye diseases. Observational and clinical trials support the safety of higher intakes of the phytochemicals lutein and zeaxanthin and their association with reducing risks of cataracts in healthy postmenopausal women and improving clinical features of AMD in patients. Additional phytochemicals of emerging interest, like green tea catechins, anthocyanins, resveratrol, and Ginkgo biloba, shown to ameliorate ocular oxidative stress, deserve more attention in future clinical trials.

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INTRODUCTION

There is accumulating evidence that phytochemicals may be involved in the prevention and reversal of age-related eye diseases. Glaucoma, cataracts, and age-related macular degeneration (ARMD) are ocular diseases that disproportionately affect persons over the age of 60 years worldwide and are recognized as the three leading causes of blindness for this population group. Based on the 2000 United States Census, there were 937,000 blind persons over the age of 40 years, with the number projected to rise to 1.6 million by the year 2020. Further estimates indicate that by the year 2020, 2.95, 3.36, and 30.1 million persons will be diagnosed with ARMD, glaucoma, and cataracts, respectively.¹

Knowledge of a relationship between nutrition and age-related eye diseases is not novel.² Elevated plasma levels of antioxidants have a protective benefit against oxidative stress, which has been implicated as the major contributor to the development of each of these ocular disorders.³–¹⁰ Nutritional therapies involving phytochemical interventions are emerging as being potentially effective in reversing the progression of age-related eye problems (Figure 1).¹¹ However, the exact mechanism of their beneficial effect in eye diseases is unknown and continues to be explored.¹² With rising public interest in phytochemicals and health and the increasing use of phytochemicals in complementary and alternative medicine (CAM) therapies, ophthalmologists, physicians, dietitians, and medical researchers need to be better informed about the evidence supporting the specific benefits and risks of particular phytochemicals prior to issuing suggestions to patients.¹³ Determining evidence-based nutritional guidelines for the efficacy of such therapies as treatments for these diseases is imperative.¹⁴

The majority of research performed to date has examined the effects of commonly known antioxidants such as vitamins E, C, and A, and carotenoids (lycopene, lutein, and zeaxanthin). Limited research trials have been conducted with other promising phytochemicals with antioxidant and anti-inflammatory properties including flavonoids (catechins, Ginkgo biloba, bilberry, grape seed extract, green tea), anthocyanins (bilberry, blueberry, black currant), and stilbenes (resveratrol).¹⁵–¹⁹ This review focuses on recent data on the role of phytochemicals in the prevention and improvement of age-related eye diseases, their defined mechanisms of action, and future applications.
ANTIOXIDANTS AND EYE HEALTH STUDIES

Observational studies

Epidemiological studies such as The Wisconsin Beaver Dam Eye Study, The Australian Blue Mountain Eye Study, The Nurses Health Study, and The Physicians Health Study have explored the relationship between the commonly known antioxidants vitamin C, vitamin A, and carotenoids and age-related eye diseases. Vitamin C showed no association with cataract risk in the Beaver Dam Eye Study, Blue Mountain Eye Study, or Physicians Health Study, whereas the Nurses Health Study showed supplementation with dietary vitamin C for >10 years contributed to a 45% decrease in the incidence of cataract surgery. Supplemental dietary intake of vitamin A showed protective benefits against cataracts in the Blue Mountain Eye study, but dietary intake of vitamin A provided none in the Nurses Health Study. Dietary intakes of the carotenoids lutein and zeaxanthin produced protective benefits against cataracts in the Beaver Dam Eye Study and the Nurses Health Study. Lutein levels were associated with the decrease in cataracts in the Beaver Eye Dam Study, and the Nurses Health Study had a 22% decreased risk of cataract with zeaxanthin and lutein intake.

Overall, then, in these four studies the reported findings concerning an association between these nutrients and carotenoids and cataract risk were inconsistent, and the scope of the potential dietary phytochemicals investigated was limited. Surveys such as the National Health and Nutrition Examination Survey have also yielded inconsistent results, with vitamins E and A having no associated benefits with cataracts, and a 1 mg/dl serum increase of vitamin C resulting in a 26% reduced risk of cataracts. Similarly, the Nurses Health Study and the Health Professionals Follow-up Study, which examined the dietary intake of antioxidants such as vitamins A, E, and C and the carotenoids lutein and zeaxanthin, did not produce strong associations between the amount consumed and risk for glaucoma.

Supplementation trials

Several clinical trials, such as the Age-Related Eye Disease (ARED) study, the Vitamin E, Cataract and Age-Related Maculopathy Trial (VECAT), and The Alpha-Tocopherol, Beta-Carotene (ATBC) study, have investigated the effects of antioxidant supplementation on eye health and yielded inconsistent findings. The beneficial effect of alpha-tocopherol and beta-carotene supplementation on the prevention of ARM was found in the VECAT and ATBC trials. In the ARED study, treatment with an antioxidant combination of vitamin C, vitamin E, beta carotene, and zinc, did produce a 25% reduction in ARM progression. The Linxian Cataract Study and the Roche European American Cataract Trial (REACT), which
examined the effect of multivitamin supplementation on cataracts, yielded inconsistent findings. In the REACT trial, a supplement of beta-carotene, vitamin C, and vitamin E produced reduced rates of cataract progression. In the Linxian Study, a multivitamin containing the same ingredients and others had no effect on reducing the prevalence of cataracts.

ETIOLOGY OF AGE-RELATED EYE DISEASES

Oxidative stress as a risk factor

Endogenous aerobic metabolism is common in all age-related eye diseases characterized by oxygen reduction. This is characterized by the initiation of the reactive oxidative intermediates, hydrogen peroxide (H$_2$O$_2$), and the singlet oxygen by irradiation, aging, inadequate antioxidant status, and reperfusion injury. Membrane lipids, nucleic acids, carbohydrates, and proteins are at risk for being damaged by the reactive oxygen species. The following are the known etiologies of ARMD, glaucoma, and cataracts.

Age-related macular degeneration

Of the tissues in the human body, the retina consumes the greatest amount of oxygen. It is the site of elevated levels of ultraviolet light, which causes oxidation of docosahexaenoic acid (22:6 ω-3) and contributes to degeneration of the photoreceptors of the eye. The double bonds of this polyunsaturated fatty acid are highly susceptible to lipid peroxidation damage from radiation. The susceptibility of the retina to damage is dependent on age and geographic region.5

Glaucoma

Glaucoma is characterized by modifications in nitric oxide metabolism, vascular alterations, and oxidative damage caused by reactive oxidative intermediates. Intraocular pressure, caused by the degeneration of the Sclero Corneal Trabecular Meshwork (TM) is thought to be the primary causative factor in glaucoma. Human studies have found increased intraocular pressure and visual field damage associated with oxidative damage in the DNA of TM cells of glaucoma patients. The oxidative causative pathway has been identified by the elevated expression of the endothelial-leukocyte adhesion molecule (ELAM-1) found in the TM. ELAM-1 expression is upregulated by the inflammatory cytokine interleukin-16,8,19

Cataracts

Metabolism of H$_2$O$_2$ to hydroxyl radical, the most reactive and damaging free radical, has been identified as the primary contributor in the etiology of cataracts. Lowered glutathione concentrations and high H$_2$O$_2$ levels have been identified in cataractous lenses. Glutathione, a natural antioxidant, contributes to protection of the eye by inhibiting oxidation of sulphydryl groups in the cell membrane. Thus, when glutathione is depleted, the potential for oxidative damage increases.8

Smoking and obesity as additional risk factors for eye disease

Obesity and smoking have been identified as modifiable risk factors for ARMD, glaucoma, and cataract and may contribute significantly to other eye conditions such as diabetic retinopathy.26,33,34 Several possible pathologies have been hypothesized,35 including the associations among obesity, oxidative stress, inflammation, lipid metabolism, and a reduction of antioxidant status. In addition to the association of smoking with the previously identified risk factors for eye diseases, smoking is also associated with an increase in size and vascularity in choroidal neovascularization, a decrease in macular pigment optical density in the retina, and the formation of sub-retinal pigment epithelium deposits, which may be indicative of oxidative injury and a factor contributing to ARMD.36–38 Under conditions of excess body weight, the renin-angiotensin system is also activated, which induces superoxide production, lipid oxidation, and decreased production of erythrocyte glutathione and glutathione peroxidase. The phytochemical antioxidants lutein and zeaxanthin in the retina are affected by decreased storage and increased endogenous oxidative destruction in obesity, leading to the development of increased risks of age-related oxidative damage in the eyes.27

PROTECTIVE ROLE OF LUTEIN AND ZEAXANTHIN IN AGE-RELATED EYE DISEASES

Dietary intake studies

Recently published prospective data from the Women’s Health Study showed higher intakes of lutein and zeaxanthin were associated with significantly decreased risks of cataracts among healthy female health professionals ≥45 years of age. Information on food and supplement intakes was obtained through administration of a detailed 131-item, validated, semiquantitative, food frequency questionnaire among 35,551 study participants. Women in the highest quintiles of lutein/zeaxanthin intake (6.7 mg/day) had a significantly lower risk of developing cataracts (multivariate-adjusted relative risk 0.82) compared to women in the lowest quintile (1.2 mg/day). Significant reductions were seen in the age and treatment-adjusted
relative risk of cataract among women consuming higher numbers of servings of green leafy vegetables (0.9 and 1.4 servings/day) versus those in the lower range. Furthermore, when adjusted for other cataract risk factors, an inverse trend was observed between incidence of cataracts and higher quintiles of green leafy vegetable intake. None of the other groups and subgroups consuming fruits and vegetables showed a risk reduction that reached statistical significance, with the exception of one trend found in the higher quintiles of raw spinach intake (>1 serving/week; age- and treatment-adjusted relative risk, 0.86). This prospective study is the largest to date reporting a significant inverse trend between lutein and zeaxanthin intakes and the risk of cataracts; its follow-up period was 10 years. However, the study did not analyze any correlation between plasma carotenoids and cataract risk, which would have strengthened the evidence for lutein and zeaxanthin having a role as important antioxidants in age-related eye diseases.39

The AREDS study, conducted among 4519 participants between the ages of 60 and 80 years, of whom 3404 had clinical features of early or advanced age-related macular degeneration (AMD), found an inverse association between higher intakes of dietary lutein/zeaxanthin (1.0, 1.3, or 2.1 mg/1000 kcal) and risk reduction of advanced AMD (odds ratio 0.54, 0.68, or 0.65), when compared to controls with little or no evidence of AMD lesions.40

On the other hand, some prospective studies have reported no protective effects of lutein/zeaxanthin on age-related maculopathy. In the Blue Mountains Eye Study,41 2335 subjects greater than 49 years of age with no incidence of early age-related maculopathy were followed-up for 5 years. Upon reexamination, early AMD was detected in 8.7% of the cohort and no protective association was found between lutein and zeaxanthin intakes and incidence of early AMD. Moreover, the median lutein and zeaxanthin intakes of these subjects in the highest quintile (1.5 mg/day) were lower compared to the reported intakes with oculoprotective effects (>1.5 mg/day).39,40 A large prospective study among 77,562 women and 40,866 men of at least 50 years of age with no diagnosis of ARM at baseline, showed no significant association between dietary intakes of lutein and zeaxanthin and the risk of early AMD. The median intakes of lutein and zeaxanthin in these subjects ranged from 1.5 mg/day in the lowest quintile to 6.6 mg/day in the highest quintile.42

Interestingly, the Carotenoids in Age-Related Eye Disease Study (CAREDS) reported a significant risk reduction in the odds ratio (0.57) of AMD in women younger than 75 years with stable dietary intakes of lutein and zeaxanthin (2.6 mg/day).43 The protective effect of lutein and zeaxanthin against age-related maculopathy seems to be evident in subjects with existing features of AMD or at higher intake levels.

Thus, on the basis of the Women’s Health Study, higher lutein and zeaxanthin intake appears to have protective effects on the risk of developing cataract, while the AREDS study supports a protective role for these phytocarotenoids on the progression of AMD. Although large clinical interventions with lutein and zeaxanthin will be needed in the future to more rigorously test the hypothesis that these phytocarotenoids can affect the incidence and progression of these important age-related eye diseases, some intriguing findings are evident in some small clinical trials.

**Short-term supplementation trials of phytocarotenoids and eye disease**

A small-scale randomized clinical trial involving a total of 27 patients (mean age 65.5 ± 5.14 years) with nonadvanced AMD investigated the effect of administering a daily oral carotenoid supplement, including lutein (10 mg) and zeaxanthin (1 mg), for 1 year. While 15 of 27 took the oral antioxidant supplement for 12 months, the remaining 12 patients received no dietary supplementation during the same period. These 27 subjects were also matched with 15 age-similar healthy controls at baseline. The group receiving supplementation with antioxidants including lutein and zeaxanthin showed a significant reduction of multifocal electroretinogram impairment after 6 months in comparison to the non-treated patient group and the healthy control group. The authors suggested that these improvements could be related to the effects of antioxidant supplementation in reducing degenerative changes of retinal pigment epithelium and photoreceptors that occur in AMD. This study also suggested that lutein and zeaxanthin in combination with other antioxidants, like astaxanthin, vitamins C and E, zinc, and copper, may exert a favorable impact on macular function in AMD patients.44

In the 6–12-month Lutein Xanthophyll Eye Accumulation study involving 101 healthy Caucasian males receiving daily supplementation of either lutein (11 mg), zeaxanthin (13 mg), or a combination (10 mg lutein, 12 mg zeaxanthin), a significant improvement in macular pigment optical density responses was observed compared to placebo. This clinical trial did not report any adverse event due to the supplemental phytonutrient doses and it reported increased bioavailability, showing a 27-fold increase in plasma xanthophyll concentrations.45 In previous clinical trials, lutein and zeaxanthin were also reported to be safe at higher doses and to improve macular pigment optical density, visual acuity, and glare sensitivity.46–47

Thus, epidemiological studies and limited clinical trials provide evidence for the protective role of lutein and zeaxanthin in reducing the risks of age-related eye diseases.
diseases like cataracts and AMD. However, further clinical investigations will be needed to strengthen the basis for recommending lutein/zeaxanthin supplementation in order to reduce oxidative damage leading to age-related eye disorders.

**PHYTOCHEMICALS OF EMERGING INTEREST IN OCULAR HEALTH**

**Ginkgo biloba**

The botanical *Ginkgo biloba*, containing flavonoid glycosides, has been studied for its effects on the prevention of mitochondrial oxidative stress exhibited in glaucoma. *Ginkgo biloba* has the ability to quench free radicals and increase vasodilatation.48,49 In a 2-day, randomized, double-masked, placebo-controlled crossover trial in 15 subjects, investigators studied the effects of a single dose of 240 mg of *Ginkgo biloba* extract (GBE) on ocular blood flow. No significant improvements in retinal arterial blood flow and intraocular pressure were found. Although these investigators noted improvements in optic nerve blood flow compared with baseline, they found this to be insignificant compared with placebo. Based on the length of this trial, the researchers recommended examining the effects of GBE in patients with ocular vascular disease in a long-term clinical setting.50 A phase I, placebo-controlled trial in 15 patients investigated the effects of 40 mg of GBE administered three times per day for 2 days on ocular blood flow. GBE increased blood flow to the ophthalmic artery, while no change was observed in the placebo group.51 Another prospective, randomized, placebo-controlled, crossover trial examined the effects of 40 mg of GBE administered for 4 weeks and found improvements in preexisting visual field damage in patients, but no improvements in intraocular pressure.52

**Anthocyanins**

Anthocyanins are water-soluble flavonoid pigments that act as potent antioxidants and are known to reduce inflammation, aging, neurological diseases, cancer, and diabetes.53,54 Researchers have identified that anthocyanins have limited absorption in vivo in comparison to other flavonoids. However, studies show accumulation of anthocyanins in the brain, liver, and eye tissues in animals.18 Blackcurrant anthocyanins have been found to be widely distributed in their intact forms in the plasma, ocular tissues, and whole eye after oral and intraperitoneal administration. Four anthocyanins were identified after intravenous administration in the aqueous humor, cornea, choroid, and retina, as well as small amounts in the vitreous and lens of animal models.55 This study illustrates the potential ocular protective benefits from oral intakes of anthocyanins. Moreover, animals fed diets supplemented with blueberries, a rich food source of anthocyanins, for 4 weeks also accumulated anthocyanin in tissues of the liver, eye, cortex, and cerebellum.18

In vitro studies have demonstrated the antioxidant effects of anthocyanins through increased expression of the glutathione-related enzymes and NADPH. These natural cellular antioxidant mechanisms inhibit oxidative stress-induced apoptosis caused by H2O2.56 Investigations have been undertaken to assess the ability of anthocyanins to reduce the adverse effects of pyridinium bisretinoid A2E, an autofluorescent pigment that can accumulate in the retinal pigment epithelium and cause damage by photooxidation and changes in membrane permeability, leading to ARMD. All tested anthocyanins displayed antioxidant activity by inhibiting photooxidation and membrane permeability changes induced by pyridinium bisretinoid A2E.57 Anthocyanin-enriched bilberry extracts have also been shown to have effects on pre- and post-translational levels of oxidative stress defense enzymes heme oxygenase (HO)-1 and glutathione S-transferase-pi (GST-pi) in retinal pigment epithelium. Preincubation with bilberry extract reduced the intracellular increase of H2O2-induced free radical generation in retinal pigment epithelium. Bilberry extract inhibited the HO-1 and GST-pi proteins by 2.8- and 2.5-fold, respectively, indicating that anthocyanins and, possibly, phenolics from bilberry can initiate the natural oxidative defense mechanisms in retinal pigment epithelium.58 Dietary supplementation with 1H636 grape seed proanthocyanidin extract (GSPE) has been shown to prevent selenite-induced cataracts. Research in animal models given 100 mg/kg body weight for 1 week indicated GSPE reduced cataract development by increasing glutathione (GSH) levels in eye lenses, which suppressed malondialdehyde (MDA), a biomarker of lipid peroxidation.59 Further studies have also illustrated the role of bilberry and blackcurrant anthocyanins in inhibiting inflammatory responses of transcription factor nuclear factor-κ-B (NF-κ-B). Participants in a parallel-designed, placebo-controlled, clinical trial who were given 300 mg/day of capsules containing purified anthocyanins isolated from bilberry and blackcurrant (Medox; Miami, FL, USA) for 3 weeks displayed 15–45% reductions of NF-κ-B inflammatory markers.60

**Resveratrol**

Resveratrol, a polyphenolic antioxidant found in red wine, has protective benefits against inflammation, positive effects on reduction of tumors, and reduces reactive oxidative species in vitro and in vivo.61,62 The development of ARMD is associated with oxidative stress in...
retinal pigment epithelium. Fifty and 100 μmol/L of resveratrol reduces the in vitro proliferation of retinal pigment epithelium cells by 10% and 25%, respectively. Research has indicated that resveratrol also inhibits selenite-induced cataract in animal models. Rats were given 40 mg/kg body weight of resveratrol for 4 days. Evaluation of lenses for GSH and MDA indicated reduced cataract development frequency. Researchers also determined the presence of increased GSH and decreased MDA and erythrocytes, which supports previous findings with proanthocyanidins.

Epigallocatechin gallate

Based on electroretinogram measurements, epigallocatechin gallate (EGCG), the principal flavonoid present in green tea, confers neuroprotection of retinas injured by ischemia/reperfusion. The investigators in this study suggest that EGCG supplementation may be beneficial in the treatment of glaucoma. Data also supports the anti-cataract effects of green tea leaf extract (GTL) in the development of cataracts. GTL-treated enucleated rat lenses were subjected to oxidative stress by sodium selenite for 24 h at 37°C. In the same study, cataract was induced in an animal model by subcutaneous injection of sodium selenite. Animals treated with GTL extract for 2 days had a reduced incidence of selenite-induced cataract in vitro and in vivo.

Thus, overall, the roles of berry anthocyanins, green tea catechins, resveratrol, grape seed, and Ginkgo biloba extracts seem promising for reversing oxidative stress and inflammation-associated ocular damage and, possibly, for improving the clinical features of age-related eye disorders.

CONCLUSIONS

Oxidative stress and inflammation play a critical role in the initiation and progression of age-related ocular abnormalities. Phytochemicals appear to have a potential role in the prevention and treatment of age-related eye diseases, like cataracts, glaucoma and macular degeneration. The mechanisms of action have not been fully defined, but may include the ability of these phytochemicals to scavenge free radicals and upregulate expression of glutathione. Decreasing oxidative damage in the retina, lens, and optic nerve of the eyes, could improve the clinical features of ARMD, including macular pigment optical density, visual field damage, and optical neuroprotection.

While lutein and zeaxanthin, the principal phytochemicals in green leafy vegetables, have been shown to reduce risks of cataracts and ARMD in observational studies and clinical trials, flavonoids in Ginkgo biloba, green tea, grapes, red wine, and berries deserve further attention in future human studies. Additional research is needed to establish the efficacy of the preventive and therapeutic aspects of individual phytochemicals in age-related ocular problems. In the meantime, incorporating 2–3 daily servings of green leafy vegetables, and additional green tea, grapes, and berries in the diet may be considered a healthy dietary choice, in addition to practicing weight management and avoidance of certain unhealthy lifestyle factors, for preserving ocular health.

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