

## Bioactive Herbal Medicine Use for Eye Sight: A Meta Analysis

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### ABSTRACT

The use of chemical medications to treat eye conditions in a way that avoids causing harm is still a work in progress for modern medicine. Herbal remedies, however, may be able to solve the problems that conventional pharmaceuticals have. Given their efficacy, lack of adverse effects, and inexpensive cost, there have been extensive efforts to discover novel medicinal plants from various locations. Several plant species have been promoted in Traditional Indian Medicine for their ophthalmic effects, and it is estimated that around 200 plants worldwide have been documented to support therapy of eye problems. This review seeks to shed light on the history of using various plants to treat eye illnesses, the advantages and disadvantages of those approaches, and the advantages of modern medicine over those of the plants themselves. Based on the findings of this review, the most effective Ayurvedic preparations may be created by combining traditional knowledge with modern techniques and polymers.

**Keywords-** Conventional drugs, Eye disorders, Herbal medicine, Traditional treatment.

### I. INTRODUCTION

Concerns about ADME (absorption, distribution, metabolism, and elimination) must be taken into account while designing a medication delivery method. Opportunities and challenges in drug distribution in the eye are distinct. One of the most fascinating and difficult tasks facing pharmaceutical researchers is the delivery of drugs to the eye. [1] Maintaining a therapeutic level at the site of action for an adequate amount of time is a challenge when administering medication to the eye. The goal of this research is to discover new delivery technologies so that a prolonged and controlled release strategy can be developed. Inserts, biodegradable polymeric systems, and collagen shields are just a few of the newer,

sensitive, and effective ocular administration systems being developed to improve ocular bioavailability and sustain the action of ocular medications. [2] Ocular inserts, which embody the controlled-release principle, are thus an appealing alternative strategy for the challenging challenge of extending pre-corneal drug residence time. The composition and intended use of an insert determines the insert's variety. Ocular inserts, which are solid devices inserted into the eye's cul-de-sac, have many benefits over liquid versions. The effective drug concentration in the eye can be ensured over a protracted time period because to the devices' prolonged retention and regulated release. There is less potential for systemic adverse effects and more precision in dosing. The ophthalmic insert can be kept in place for up to seven days by being inserted into the third eyelid of

mammals. Isolation of active chemicals from plants, such as morphine from opium, marked the beginning of modern drug development in the nineteenth century [1]. Herbal remedies were used in the early stages of glaucoma treatment; however, their preparation was sometimes rudimentary and based on trial-and-error [2]. Pilocarpine was first used to treat glaucoma, and it is a parasympathomimetic alkaloid found in the South American shrub *Pilocarpus microphyllus* [3]. Since pilocarpine stimulates ciliary muscle contraction, it improves aqueous humour drainage through the trabecular meshwork at the iridocorneal angle [4]. Modern anti-glaucoma medications with lower risk profiles have led to a drop in the use of pilocarpine for glaucoma therapy, but it is still available.

While pharmaceutical companies still extract useful chemicals from plants used in traditional medicine, this is done in a more systematic fashion these days. The Food and Drug Administration (FDA) is in charge of enforcing these regulations in the United States (FDA). Alternative treatments, such as herbal medicines and nutritional supplements, are not governed by the FDA [6]. This results in a large difference in the purity and potency of these agents on the market, as no safety or efficacy trials are necessary to offer these drugs.

When it comes to irreversible vision loss and blindness, glaucoma is by far the most common cause worldwide [7]. Standard treatment for glaucoma now involves reducing intraocular pressure (IOP) with medication, laser therapy, or surgery [8]. But natural remedies like herbs and vitamins and minerals are on the rise. Up to 52% of the population uses some form of alternative medicine [9,10], creating a global business of \$109 billion.

Ginkgo biloba, bilberry, and marijuana are often used herbal therapies for glaucoma [11-13], despite the lack of controlled research studies on herbal medicines. Thirteen percent of glaucoma patients in a sample of 1516 reported using complementary or alternative medicine to treat their condition. More over 40% of these patients believed that the medications were treating their glaucoma, and nearly two-thirds had not mentioned this fact to their ophthalmologist [11]. The majority of these people got their information on alternative medicine from the media and friends and family, which are not always credible sources and can put people at risk [11].

## II. MATERIAL & METHODS

Given the popularity of herbal remedies and the fact that many patients do not feel comfortable discussing their use with their doctors, it is crucial that ophthalmologists and other eye care professionals inform their glaucoma patients about the therapeutics, safety, and efficacy of commonly used herbal remedies. This article's goal is to look at the data supporting the

most popular herbal medications for glaucoma therapy and discuss the negative side effects of these drugs. PubMed, Google Scholar, and the Cochrane Library were used to search for relevant literature.

## III. HERBAL PLANTS WHICH USED IN EYE CARE

**Curcumin:** The spice curcumin, often called *Curcuma longa*, plays a significant role in the cuisines of South Asia. It has a long history of usage against inflammatory illnesses, and it is derived from the turmeric plant. Curcumin is a lipophilic polyphenol, meaning it is insoluble in water, yet it can be stable in low-pH conditions like the human stomach. Curcumin's processes rely on its interplay with a wide variety of inflammatory-targeting molecular determinants. The enzymes cyclooxygenase-2 (COX-2), lipoxygenase, and inducible nitric oxide synthase (iNOS) are all under its control, which allows it to modulate inflammatory processes. Interleukins, monocyte chemoattractant protein (MCP), and migration inhibitory protein are all inflammatory cytokines that curcumin blocks in its production. Curcumin is an anti-inflammatory and anti-oxidative agent, so we tested it on a rat model of light-induced retinal degeneration (LIRD) and on cell lines derived from the retina to see if it could slow the progression of the disease. In rats fed a diet containing 0.2% curcumin for 14 days, we saw improved neuroprotection in the retina [28]. Curcumin's ability to suppress NF-kappa B activation and reduce expression of inflammatory genes provided retinal protection against light-induced retinopathy of the eye (LIRD). Curcumin has been shown to protect retina-derived cell lines from hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>)-induced cell death by activating cellular protective enzymes including HO-1 and thioredoxin, according to experiments using 661W and ARPE-19. Curcumin's cytoprotective properties against H<sub>2</sub>O<sub>2</sub> oxidative stress were shown to be boosted by 15 M after incubation with human retinal cells, with the reduction of reactive oxygen species (ROS) levels mediating an increase in HO-1 expression. Curcumin's capacity to regulate the expression of cellular regulatory proteins like NF-B, AKT, NRF2, and growth factors also contributes to its anti-inflammatory and cellular-protective effects. Curcumin's direct effects on ocular disorders have been demonstrated in several in vivo rat model studies. Curcumin's preventive benefits against streptozotocin-induced diabetic retinopathy in Wistar albino rats have been demonstrated in recent DR research. Curcumin has also been shown to prevent cataracts from forming in rat models of galactose toxicity, naphthalene toxicity, selenite toxicity, and diabetes. Curcumin supplementation in the diet also protected the lens of diabetic rats from developing a cataract by reducing the loss of chaperone-like activity of lens -crystallin. Curcumin has showed promise as a potential natural treatment, but it has also been

demonstrated to cause harmful side effects on a consistent basis since 1976. Changes to DNA and chromosomes are the most notable side effects of curcumin, especially at higher concentrations. Curcumin's anti-oxidative and anti-inflammatory qualities still make it a chemical of choice in the treatment and prevention of AMD, DR, and cataract, despite the risk for negative effects at high doses.

**Saffron:** Medicinal plants and herbal products are widely used for the treatment of various diseases, but their potential use in the treatment of eye disorders has received less attention. An optimal medication schedule and treatment plan is suggested due to the significance of eye diseases and the impact of treatment method on visual acuity. The low risk associated with herbal medicines and other therapeutic approaches leads to greater patient acceptance. Because of this, the pharmacological properties of herbal medicines have been the subject of increased study. Mechanism studies of crocin's retino-protective effects have shown that it activates the PI3K/AKT signalling pathway, which in turn reduces oxidative stress, inflammation, and cell apoptosis. In addition, crocin's neuroprotective, antiphotodamage, and cytoprotective effects were demonstrated in animal studies, resulting in enhanced visual activity, protection of retinal photoreceptors, and inhibition of oxidative stress in the rat eye. The mitochondrial route, activation of nuclear factor kappa B (NF-kappa B), and suppression of reactive oxygen species (ROS) and lactate dehydrogenase (LDH) have all been proven to play a role in crocin's protective effects on retinal ganglion cells against H<sub>2</sub>O<sub>2</sub>-induced ischemia. Because of its neuroprotective properties, crocin also prevents the death of retinal photoreceptors in response to exposure to light. Another study found that saffron prevented apoptosis and decreased ATP-induced intracellular calcium in eye cellular photoreceptors at a level of 5 mg/kg. However, by blocking caspase activity, crocetin protected cells in the mouse model's eye against degeneration. Safranal, another component of saffron, has been found to prevent cell death due to oxidative stress in the eyes of rats. Researchers found that saffron enhanced fERG in the eyes of rats by mechanisms including CB1 and CB2 receptor antagonism and its neuroprotective effect, but crocin had no such effect. Saffron at 25 mg/kg and crocin at 100 mg/kg prevented alpha-crystallization and glycation and enhanced visual acuity in mice and rats via lowering oxidative stress. Eye photoreceptor shape and function are both improved by saffron, which also protects the retina from oxidative stress in rats. In Wistar rats, it was found to be effective in preventing cataract development at a level of 60 mg/kg by protecting eye cells against selenite-induced cataract (selenite depletion), lipid peroxidation, superoxide dismutase (SOD), and malondialdehyde.

**Green team:** The anti-oxidative effects of GTE and EGCG in age-related macular degeneration have been

the subject of a number of investigations (AMD). Research has linked genetic variation in CFH, a key regulator of the complement system in innate immunity, to the development of AMD. Intraocular injection of sodium nitroprusside caused oxidative damage to retinal photoreceptors. Significant decreases in visual function, as measured by ERG a- and b-wave amplitudes, were observed following injection. After sodium nitroprusside injection, RT-PCR and Western blotting showed decreased expression of photoreceptor-specific markers RET-P1 and rhodopsin kinase and increased expression of the cell death marker caspase-3. Co-injection of EGCG with sodium nitroprusside greatly attenuated these adverse effects in the retina. Oxidative stress may contribute to the development of chronic inflammation. GTE's antioxidant effects on a retina-specific oxidative stress animal model were studied. By administering sodium iodate intravenously, they caused oxidative degeneration of the retina in rats. Pathological abnormalities of the retina caused by sodium iodate were seen in the in vivo imaging by cSLO and SD-OCT, particularly in the inner nuclear layer, outer nuclear layer, and retinal pigment epithelium layer. Through the use of imaging techniques, they discovered that GTE dramatically reduced the severity of the retinal lesions.

**Ginkgo biloba:** Ginkgo biloba extract (GBE) has a therapeutic effect on glaucoma sufferers by increasing blood flow to the eyes, which may help alleviate the disease's symptoms. Blood flow in the eyes was evaluated both before and after treatment with colour Doppler imaging. Washout periods of two weeks separated GBE from placebo. Ophthalmic artery (OA) end diastolic velocity (EDV) was considerably raised by ginkgo biloba extract compared to placebo (baseline vs GBE-treatment; 6.5 0.5 vs 7.7 0.5 cm/sec, 23 percent change, p=0.023). Results showed that GBE was safe and had no adverse effects. There was no change in arterial blood pressure, heart rate, or intraocular pressure after taking a ginkgo biloba extract. More research into ginkgo biloba extract's effects on ocular blood flow and neuroprotection is warranted so that it can be used to treat glaucomatous optic neuropathy and other ischemic ocular illnesses.

**Ginseng:** Among the various organs diabetes mellitus (DM) can damage, the eyes are a major concern. Diabetic retinopathy (DR), diabetic macular edema (DME), cataracts, and glaucoma are only a few of the degenerative eye ailments that make up diabetic eye illnesses. Diabetic retinopathy (DR) is the leading reason for blindness in people with diabetes. Vision distortion and fluid leakage are the results of high blood glucose damaging the wall of small blood vessels in the retina. Scars and retinal detachment precede permanent vision loss in advanced DR due to the formation of new, fragile blood vessels on the retina. Many physiological abnormalities, such as elevated levels of tumour necrosis factor-alpha (TNF-), interleukin (IL)-1, vascular endothelial growth factor (VEGF), IL-8, and IL-6, have

been detected in the retina or vitreous humour of diabetic animals and humans, supporting the hypothesis that chronic inflammation is a hallmark of DR. Accordingly, antiinflammatory therapy in addition to standard DR treatment, such as glycemic control, laser surgery, vitrectomy, and anti-VEGF medication, might be effective for the prevention or delay of disease progression. Researchers have looked into the healing properties of ginseng and ginsenosides for DR more than any other ocular illness. It has been hypothesised that TNF- may indirectly stimulate angiogenesis by elevating VEGF expression. Ginsenoside Rg3, when given intragastrically to diabetic rats, reduced VEGF and TNF-expression in the inner nuclear layer and ganglion cell layer of the retina. As indicated before, ginsenoside Rb1 also suppressed VEGF secretion from mature RPE cells, which suggests that ginsenoside Rb1 might have favourable effects on DR and AMD by reducing retinal neo vascularization.

**Salvia miltiorrhiza:** There is a significant problem with glaucoma-related retinal degeneration and blindness in Asian countries, especially among the elderly. Infusion of trophic nutrients, electrical stimulation, and visual training are just few of the methods used to boost retinal neuron survival after an increase in intraocular pressure. In several models of neuronal injury, including glaucoma-induced cell loss, extracts from traditional medicine, particularly herbal medicine, have been demonstrated to increase the survival of RGCs. This study fed a *Salvia miltiorrhiza* extract to a rat model of glaucoma to examine the extract's potential protective benefits in glaucoma. Furthermore, *Salvia miltiorrhiza* has been employed as part of a formulation to treat diabetic retinopathy and glaucoma-related retinal degeneration. Among the several bioactive compounds found in *Salvia miltiorrhiza* are danshensu (DSS), protocatechuic aldehyde, salvianolic acid B, cryptotanshinone, and tanshinone. One of the most crucial elements, DSS may be responsible for the neuroprotective effects seen in the retina and is thus often regarded as a key factor. There is a need for more research into the bioactive components of *Salvia miltiorrhiza* and whether or if purified DSS at varying doses displays neuroprotective benefits in glaucoma and other eye ailments.

#### IV. LUTEIN AND ZEAXANTHIN

Carotenoids such as lutein and zeaxanthin are abundant in tomatoes, Chinese wolfberry fruit, and carrots because they are members of the xanthophyll family. They differ by a double bond and are therefore considered to be isomers (Fig. 1). However, zeaxanthin only has one chiral centre, while lutein has three. 21 Zeaxanthin is a symmetrical compound, with no discernible difference between its (3R,30S) and (3S,30R) stereoisomers. Since this is the case, zeaxanthin only comes in three different stereoisomers.

Zeaxanthin (3R,30R) is the predominant form found in nature. 22 There are two pyridinium bisretinoid byproducts created from all-trans-retinal in the visual cycle; these are A2-PE and A2E. (Fig. 2). 23 Zeaxanthin, which is more powerful than alpha-tocopherol, prevents ARPE-19 from being damaged by photooxidation. Combining zeaxanthin with alpha-tocopherol increases its efficacy. 24 Zeaxanthin functions as a photo filter, soaking up light and blocking the production of reactive oxygen species (ROS) and the antioxidant 5a-tocopherol-OOH. Zeaxanthin can be regenerated with the help of antioxidants like ascorbic acid or alpha-tocopherol. Retinal zeaxanthin was found to have a significant inverse correlation with the number of apoptotic rods and cones in a light-damaged quail eye, showing that it protects photoreceptors from light-induced damage. 25,26 Diabetic rats that were given zeaxanthin supplements had their DNA, electron transport complex III, nitrotyrosine, and mitochondrial superoxide dismutase protected from oxidative stress. 27 Diabetic patients' retinal expression of vascular endothelial growth factor and intercellular adhesion molecule-1 was also suppressed. 27 Furthermore, lutein shields the retina from the oxidative stress caused by diabetes. 28 In a laser-induced choroidal neovascularization mouse model, 3 days of oral lutein pretreatment significantly reduced choroidal neovascularization compared to vehicle. The expression of inflammatory-related molecules like vascular endothelial growth factor, monocyte chemotactic protein-1, intercellular adhesion molecule-1, IκB-α degradation, and NF-κB p65 translocation was inhibited, as was macrophage infiltration into the choroidal neovascular membrane. 29 The Age Related Eye Diseases Study also demonstrated that lutein and zeaxanthin intake was related with a reduced risk of AMD<sup>30</sup>. Odds ratios of 0.65, 0.45, and 0.73 indicate that consuming dietary lutein or zeaxanthin can reduce the incidence of age-related macular degeneration, geographic atrophy, and big or extensive intermediate drusen. 31 But in prospective research with a 7-year follow-up, they were found to be positively linked with AMD progression (odds ratio 2.65, 95% confidence range 1.13e6.22). That's why it's hard to draw firm conclusions about whether lutein or zeaxanthin would help with age-related macular degeneration in a clinical setting.

#### **Omega-3 fatty acids**

Omega-3 fatty acids are long-chain polyunsaturated fatty acids that have a common final carbon-carbon double bond between the last third and fourth carbon of the fatty acid chain (Fig. 3). They are essential fatty acids, which mean essential for health maintenance. However, they must be obtained from diet, because the body cannot synthesize them. Common sources from plants include algal oil, flaxseed oil, and sea buckhorn seed.<sup>33</sup> Docosa-hexaenoic acid (DHA), all-cis-docosa-4,7,10,13,16,19-hexaenoic acid

[22:6(n-3)], has 22 carbons with six conjugated double bonds. Eicosapentaenoic acid (EPA), (5z, 8z, 11z, 14z, 17z)-eicosa-5,8,11,14,17-pentenoic acid [20:5 (n-3)], has 20 carbons and five conjugated double bonds. These omega-3 fatty acids are extensively studied in ocular health maintenance. DHA is the major fatty acid constituted in the outer segment disc membrane of

retinal photoreceptors. The bio-physical and biochemical properties of DHA can affect the integrity and function of the membrane through altering the permeability, fluidity, thickness, lipid phase properties, and activation of membrane-bound proteins, which subsequently affect the photo-transduction and vision.<sup>34</sup>

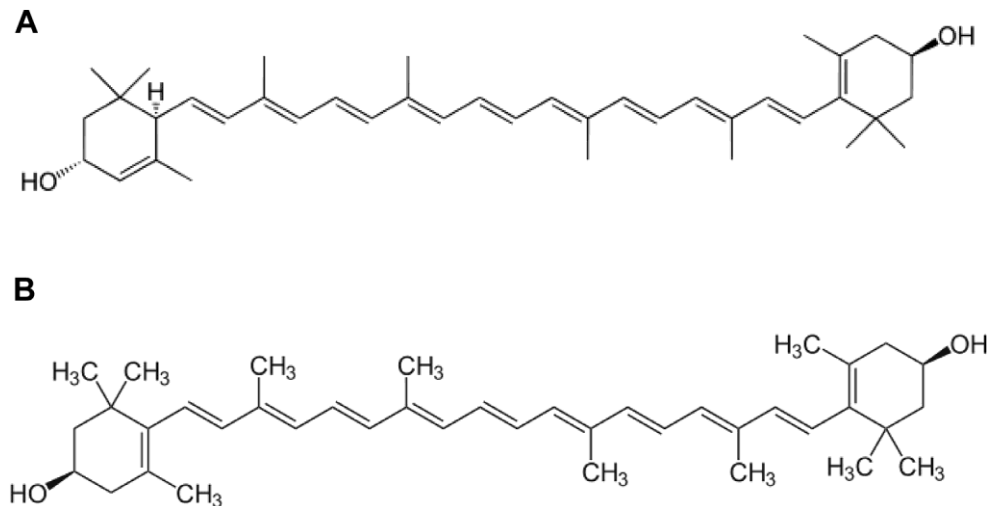


Fig.1: Structure of (A) lutein; (B) zeaxanthin.

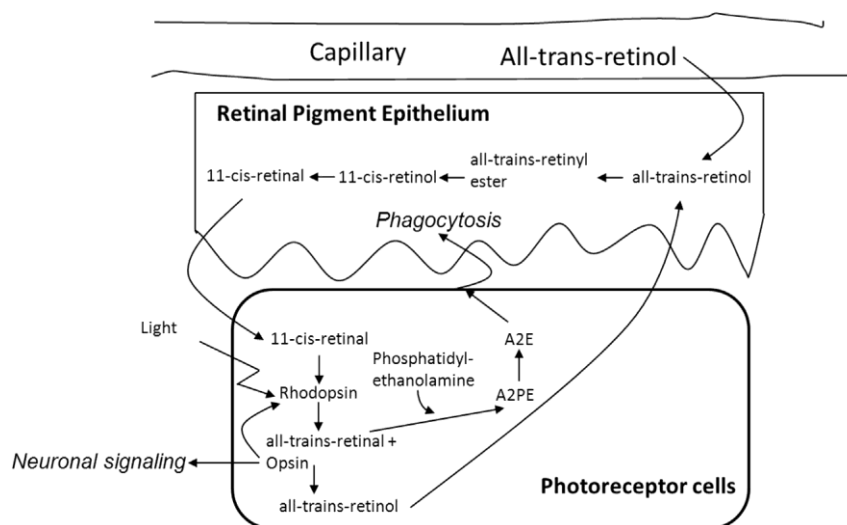


Fig. 2: Visual cycle and A2E formation. A2E is formed from all-trans-retinal when it reacts with phosphatidylethanolamine in the visual cycle in the photoreceptor outer segments. Precursor A2-PE is formed. After a multi-step biological process, A2E is released following phosphate hydrolysis [23].

Omega-3 fatty acids also act as antioxidants. Their poly-unsaturated conjugated bonds provide a sink to absorb electrons from reactive species. They remove electrons from free radicals through formation of peroxides, to protect cell membranes and other macromolecules from attack. It has been reported that omega-3 fatty acids prevented free radical-induced hemolysis,<sup>35</sup> abnormal *in vitro* low-density lipoprotein oxidation,<sup>36</sup> excessive superoxide anion

generation,<sup>37,38</sup> and oxidative stress. In addition, DHA also reduced caspase-3 expression and genomic DNA fragmentation in serum-starved PC-12 and Neuro-2A cells, thereby inhibiting the apoptosis of neuronal cells.<sup>40</sup> DHA inhibited photoreceptor cell apoptosis, prolonged its survival *in vitro*, and promoted differentiation of developing photoreceptors.<sup>42</sup> DHA treatment reduced Bax and increased bcl-2 expression, protected mitochondrial membrane structure, and

preserved photoreceptors from apoptosis when the rat photoreceptors were exposed to paraquat *in vitro*.<sup>43</sup> Several epidemiology studies examined the relationship between omega-3 fatty acids or fish intake with prevalence of age-related macular degeneration. A systematic review with 88,974 people showed the amount of omega-3 fatty acids or fish consumption largely associated with decreased risk of age-related macular degeneration.<sup>6</sup> Increased omega-3 fatty acids consumption correlated with decreased occurrence of late age-related macular degeneration development, with an odds ratio of 0.62 and 95% confidence interval 0.48e0.82. Consumption of fish more than twice a week was also associated with a decreased risk of occurrence of both early age-related macular degeneration (odds ratio 0.76) and late age-related macular degeneration (odds ratio 0.67).

## V. CONCLUSIONS

One such health and longevity practise passed down through the generations is Ayurveda. Ocular illnesses can be effectively treated with a wide range of plants. Ocular illnesses are treated with a variety of plants, and their uses are documented in this article. Researchers are aided by this summary in their quest to find better treatments for eye diseases; these advancements will ultimately benefit society at large.

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