Herbal Medicines in Glaucoma Treatment

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INTRODUCTION

Drug discovery in the modern era began in the 19th century with the isolation of active compounds from plants, such as morphine from opium [1]. The early treatment of glaucoma relied on herbal remedies, but the preparation of these medicines were crude and empirical [2]. One of the first medicinal plants used for glaucoma was pilocarpine – a parasympathomimetic alkaloid extracted from a South American shrub, \textit{Pilocarpus microphyllus} [3]. Pilocarpine causes the contraction of the ciliary muscles, which facilitates the aqueous humor outflow through the trabecular meshwork at the iridocorneal angle in the eye [4]. Although pilocarpine is still available for glaucoma management, its usage has declined due to the availability of modern anti-glaucoma drugs with safer side effect profiles [5].

Today, although the pharmaceutical industry continues to isolate active compounds from medicinal plants, it is achieved using standardized techniques. In the US, these standardized practices are enforced by the Food and Drug Administration (FDA). The FDA regulates prescription drugs and over the counter drugs, but not alternative medicines, such as herbal medicines and nutritional supplements [6]. A major consequence is that neither safety nor efficacy studies are required to sell these medicines,
and this contributes to the significant variation in purity and potency of these agents on the market.

Glaucoma is the leading cause of irreversible visual impairment and blindness worldwide [7]. Current standard of care for glaucoma is to lower the intraocular pressure (IOP) through medical, laser, and/or surgical therapy [8]. However, the use of alternative therapies like herbs, vitamins, and minerals is becoming more popular. Alternative medicines have a global market of $109 billion and are widely used by up to 52% of the general population [9,10].

Despite the paucity of controlled research studies on herbal remedies, a subset of the population uses herbal remedies for their glaucoma and among the most commonly used are *ginkgo biloba*, bilberry, and marijuana [11-13]. In a survey of 1516 glaucoma patients, 13.7% reported current or previous use of alternative medicines for their glaucoma [11]. Notably, nearly two-thirds of these patients had not disclosed to their ophthalmologist of their alternative medicine use, and more than 40% believed that the treatments were helping their glaucoma [11]. The majority of these patients learned about alternative medicines through media and relatives, which are not always reliable sources and could put patients at risk [11]. Given the widespread use of herbal medicines and the tendency of patients to not disclose their use to their providers, it is important for the eye care professionals to educate their glaucoma patients on the therapeutics, safety, and efficacy of commonly used herbal medicines. The purpose of this article is to examine the evidence surrounding the most commonly used herbal medicines in glaucoma treatment and review the adverse effect of these agents. Literature search was conducted through the databases including PubMed, Google Scholar, and Cochrane Library.

**THERAPEUTIC AND ADVERSE EFFECTS OF HERBAL REMEDIES**

**Ginkgo (Ginkgo Biloba)**

_Ginkgo (Ginkgo Biloba)_ extract (GBE) is processed from the leaves of a tree that originated in China over 250 million years ago. GBE is comprised mostly of flavonoids and terpenoids and contains over 60 bioactive compounds, 30 of which are not found anywhere else in nature [14]. Additionally, it is the most commonly used herbal supplement by elderly patients [15].

Although the mechanism of glaucoma is still largely unknown, oxidative stress, optic nerve ischemia, and neuroinflammation were found playing certain roles in the development of glaucomatous optic nerve degeneration [16-22]. It has been suggested that GBE may protect tissue against free radical damage like other antioxidants such as Vitamin C and E. However, unlike the others, GBE acts at the level of organelles by stabilizing the mitochondria. Abnormal mitochondrial changes can make the retinal ganglion cells more susceptible to oxidative stress [23-25]. One study found GBE could decrease the level of reactive oxygen species and protect the mitochondrial membrane in cultured neuronal cells [26]. GBE was also found to have vasodilatory properties that could improve coronary and peripheral circulation [27], and rheological effects that could improve blood viscosity [28]. In addition, GBE can reduce active cells (e.g., glial cells) in low grade inflammation [29]. Due to its antioxidant, vasoregulatory, and anti-inflammatory benefits, GBE is considered a neuroprotective agent and has been proposed for the treatment of glaucoma.

Four randomized control trials (RCT) have been conducted to examine the effect of GBE on glaucoma. The first was a double masked crossover study on normal tension glaucoma (NTG) patients with two treatment groups of either 4 weeks of GBE administration with 8 weeks placebo or reversed order [30]. Visual field (VF) indices were statistically improved after GBE supplementation compared to baseline, but the improvement was not maintained after the washout and no significant changes in IOP. However, these findings were not replicated in a similar cross-over study done by Guo et al. who found no significant differences in VF indices and IOP [31]. Both studies had the same treatment sequence and duration, but the latter recruited patients with newly diagnosed NTG on topical hypotensive agents. Another contributing factor could be the ethnic differences between the patient populations, as the initial study was conducted with a European population, while the later study with an Asian population.

Another RCT demonstrated desirable effects of GBE on blood flow in NTG. Specifically, significant increases in ocular blood flow, blood volume, and velocity were shown after 4 weeks of GBE supplementation in comparison to placebo [32]. Lastly, Dewi Sari et al. examined effects of GBE in primary open angle glaucoma (POAG) patients after 6 months of GBE administration in comparison to placebo and reported significant improvement in VF indices, superior and inferior retinal nerve fiber layer thickness, malondialdehyde (plasma derived oxidative stress marker), and glutathione peroxidase (antioxidant enzyme), but no significant changes in IOP [33]. However, whether the improvement between the treatment group and baseline was significant is uncertain.

Generally, ginkgo is well tolerated [34], but the most severe adverse effects of GBE are related to its anti-thrombotic properties. Some case reports identify ocular complications such as retinal hemorrhage and hyphema, while systemic effects as subarachnoid hemorrhage and subdural hematoma [6]. However, two RCTs examining the
effect of GBE on elderly patients demonstrated that the incidence of bleeding between patients taking GBE and those taking placebo is not significantly greater [35,36].

Bilberry (Vaccinium myrtillus)
Bilberry is a medicinal fruit that has been used since the 16th century [37]. In a survey of glaucoma patients using herbal remedies for treatment, about 50% reported using bilberry [12]. The active component in bilberry is anthocyanin, which is a flavonoid [3]. Similar to GBE, the proposed therapeutic effect of bilberry is established on its potential neuroprotective function for the neurodegenerative process in glaucoma, by improving retinal ganglion cell profusion, stabilizing optic nerve structure, enhancing the resistance of retinal ganglion cells to the mechanical or ischemic alteration, and decrease neuroinflammation. Multiple mechanisms of actions of bilberry have been suggested (Table 1): 1) antioxidative properties [38]; 2) decreased capillary fragility [39]; 3) collagen stabilization and promotion of collagen production [40]; and 4) prevention of proinflammatory compound production and release [39].

Given the favorable effects of bilberry on antioxidation and blood circulation, it has been studied for the treatment of glaucoma. A controlled retrospective study examining the effects of bilberry and GBE supplementation for 6-59 months observed improved visual acuity in those receiving supplementation, but a deterioration in visual acuity in the control group [41]. Additionally, an improvement in VF was noted, however there was no significant difference between the changes seen in VF of treatment and control groups [41]. No effect on IOP was found by bilberry supplement use. An RCT with 24 months of anthocyanin supplementation reported a decrease in VF mean deviation, however the decrease in mean deviation was significantly less in the treatment group in comparison to placebo group [42].

In the above studies, no side effects were reported from the use of bilberry. On the other hand, cachexia, anemia, and icterus may occur with bilberry overdose [3].

Marijuana (Cannabis sativa)
Marijuana, also known as cannabis, has been used for medicinal purposes for thousands of years, yet has had a complicated history of acceptance in Western medicine [43]. In 1937, marijuana was criminalized in the United States. California was the first state to legalize the medical use of marijuana in 1996. Since then, 32 other states and the District of Columbia have also authorized the use of medical marijuana [44]. With the steady legalization of marijuana and a positive shift in its social acceptability, glaucoma patients are more likely to use marijuana as a therapeutic alternative [13].

Marijuana is composed of over 400 compounds, but the main components responsible for its physiological effects are Δ-9-tetrahydrocannabinol (THC) and cannabidiol (CBD). The mechanism of action by which marijuana exerts its ocular effect is not well understood [45]. The endocannabinoid system has two main G-protein receptors called cannabinoid receptor type 1 and 2, CB1 and CB2. CB1 suppresses neurotransmitter release at presynaptic neurons and is found on the ciliary body and muscles, trabecular meshwork, and Schlemm’s canal, suggesting it affects aqueous humor production as well as trabecular and uveoscleral outflow; while CB2 modulates cytokine release in the immune system (Table 1) [46]. Additionally, marijuana is thought to provide a neuroprotective effect by suppressing apoptosis and decreasing free radicals [47].

Hepler and Frank investigated the efficacy of smoking marijuana in a small number of normal volunteers and reported a ~30% reduction in IOP [48]. However, only 60-65% of individuals would experience this effect [49]. The duration of the pressure lowering effect is relatively short, 3-4 hours. THC can be administered through various routes including inhalation, oral, sublingual, intravenous, and topical. Counterintuitively, topical application is the least optimal route of administration for glaucoma.
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CURRENT TREATMENTS FOR GLAUCOMA

Glaucoma is a group of optic neuropathies that involve progressive death of retinal ganglion cells, degeneration of the optic nerve and ultimately, defects in visual field [59]. Primary open angle glaucoma is the most common type and it differs from normal tension glaucoma in the former, elevated IOP occurs [60]. Left uncontrolled, glaucoma has irreversibly devastating visual consequences. Current treatment typically involves topical ocular hypotensives as first line therapy and the six major drug classes are as follows: ß-adrenergic blockers, α2-adrenergic agonists, prostaglandin analogues, carbonic anhydrase inhibitors, rho kinase inhibitors, and cholinergic agonists [61-63]. These work to lower IOP by preventing aqueous humor build up in the anterior chamber via decreasing aqueous humor production from the ciliary body or increasing aqueous humor outflow through the trabecular meshwork or uveoscleral pathway. Despite being on a combination of eye drops, patients may fail to achieve goal IOP reduction and laser or surgical interventions are considered. Although high IOP is a risk factor for glaucoma progression, glaucomatous optic neuropathy can occur in individuals with normal IOP [60]. Thus, interventions that focus solely on IOP reduction may not be beneficial for some glaucoma patients.

Considered by some to be a complementary or alternative therapy, neuroprotective treatment is another approach for glaucoma management [16,64]. Neuroprotection in glaucoma focuses on the prevention or slowing of death and deterioration of retinal ganglion cells [65]. Potential neuroprotective agents existing in nature, such as the above discussed GBE and bilberry [14,66] have increasingly drawn interest for this treatment strategy. However, high-level evidence is still lacking to prove the effectiveness of neuroprotective agents, including medicinal herb supplements, against glaucoma [66].

CONCLUSION

GBE and bilberry have been studied for glaucoma treatment due to their potential as neuroprotective agents. Both are attractive candidates as they are affordable, readily available, and relatively safe [31,67]. However, the evidence surrounding their efficacy is conflicting. Their effects on glaucomatous VF change are still inconclusive [30-33,41,42].

Medical marijuana has been shown to have favorable effects on glaucoma management through its IOP lowering ability [48]. This effect, however, is short lived and would require multiple daily doses, which puts patients at risk for developing cannabinoid use disorder. Considering the brief duration of action, extensive side effect profile, addictive potential, and lack of evidence that its use alters the course of glaucoma, medical marijuana of any form is currently not recommended as a standard of care to treat glaucoma patients.

Overall, glaucoma is a chronic heterogenous group of disorders that is not always under control with the currently available drugs. The potential of medicinal plants in the treatment of glaucoma is exciting as some can exert an effect through neuroprotection of retinal ganglion cells. However, despite the robust theoretical rationale and initial clinical evidence for the beneficial effect of GBE and bilberry as an adjunct therapy, the evidence is not conclusive. Additionally, there are no studies that investigate the effect of GBE, bilberry, and marijuana on the course of glaucoma in comparison to the pharmaceutical agents currently available. Future studies need larger
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