YALE JOURNAL OF BIOLOGY AND MEDICINE 93 (2020), pp.347-353.

MINI-REVIEW

YALE JOURNAL OF BIOLOGY AND MEDICINE
YJBM
CELEBRATING 90 YEARS 1928–2018

Herbal Medicines in Glaucoma Treatment

Maryam Ige[a] and Ji Liu[b,*]

[a]Yale University School of Medicine, New Haven, CT; [b]Department of Ophthalmology and Visual Science, Yale University School of Medicine, New Haven, CT

Glaucoma is the leading cause of irreversible blindness worldwide. Optimizing treatment is important to protecting vision. The current standard of therapy for glaucoma involves lowering the intraocular pressure (IOP) through medical, laser, and/or surgical therapy. Nevertheless, there are an increasing number of glaucoma patients that use alternative medicines to treat their glaucoma or supplement their traditional glaucoma management. Ginkgo biloba, bilberry, and medical marijuana are amongst the most commonly used medicinal plants by glaucoma patients. We reviewed the literature to determine the benefits, safety, and efficacy of these herbal remedies. Though ginkgo biloba and bilberry may prevent or slow down retinal ganglion cell death, there is no evidence yet to suggest that they alter the course of glaucoma. Medical marijuana has shown IOP lowering effect in some individuals, but its short duration of action, significant adverse effects, and addictive potential have rendered it an inappropriate standard therapeutic agent for glaucoma. Larger studies with longer durations that investigate the effect of herbal medicines on the course of glaucoma in comparison to the current standard of care are needed to elucidate their benefits in glaucoma treatment.

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, *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,

*To whom all correspondence should be addressed: Ji Liu, MD, 40 Temple St., Department of Ophthalmology and Visual Science, Yale University School of Medicine, New Haven, CT, 06510; Tel: 203-785-2020, Fax: 203-785-7090, Email: liu.ji@yale.edu, ORCID iD: 0000-0003-1240-7046.

Abbreviations: GBE, ginkgo biloba extract; THC, Δ-9-tetrahydrocannabinol; CBD, cannabidiol; VF, visual field; IOP, intraocular pressure; NTG, normal tension glaucoma; RCT, randomized control trials; FDA, Food and Drug Administration.

Keywords: Ginkgo biloba, bilberry, marijuana, glaucoma, medicinal plants, visual field, intraocular pressure

Author Contributions: MI reviewed the literature and drafted the manuscript. JL provided guidance on the topic and critical revisions to the manuscript.

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 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 antithrombotic 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

Table 1. Characteristics of medicinal plants commonly used by glaucoma patients.

Herbal Medicine	Route of Administration	Mechanism of Action	Adverse Effects
Ginkgo	Oral	Antioxidant Mitochondria stabilization Vasorelaxation Blood viscosity reduction Anti-inflammation	Bleeding
Bilberry	Oral	Antioxidant Capillary and collagen stabilization Anti-inflammation	Cachexia, anemia, icterus if overdose
Marijuana	Oral, Inhalation, Sublingual, Intravenous, Topical	IOP reduction Anti-inflammation Antioxidant	Psychotropic effects, tachycardia, hypotension, conjunctival hyperemia

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

treatment due to the poor ocular penetration of the highly lipophilic and low aqueous solubility of the cannabinoid extracts [50]. A short study revealed no difference in IOP between those who received topical 1% THC or light mineral oil (control) [51]. However, a newer topical synthetic cannabinoid, WIN55212-2, decreases IOP by 20-30% in glaucoma patients, but the maximal effect occurs at 1 hour [52]. Synthetic cannabinoids, such as BW29Y and BW146Y, were administered orally to glaucoma patients and BW146Y was as effective in lowering IOP as smoking marijuana or ingesting THC; whereas BW29Y had no significant effect [53]. Interestingly, contrary to THC, CBD was found raise IOP at 1 and 4 hours after topical administration on mouse eyes [54]. Such IOP elevating effect was also observed 4 hours after a higher dose of CBD was given sublingually in a human study [55].

The adverse effects associated with marijuana are tachycardia, hypotension, conjunctival hyperemia, decreased lacrimation, and psychotropic effects (euphoria, dysphoria, cognitive impairment, decreased short-term memory, time distortion, reduced coordination, and sleepiness) [56]. In addition, the hypotensive benefit of marijuana on IOP may be canceled by the concurrent blood pressure reduction that would potentially lead to profusion deficiency and ischemic change of the optic nerve [57,58]. Some side effects specific to the route of administration include emphysema and possible lung cancer for smoking marijuana as well as corneal injury and local irritation for topical THC [51,56]. An additional concern is warranted for the potential addictive properties and tolerance [50]. This is especially concerning because in order to achieve 24-hour IOP control with marijuana, patients will have to smoke about 6-8 times daily, which is likely to lead to cannabinoid use disorder [50]. In order to maintain this dose, the expected cost is about $690 per month, which is significantly more than the current medications [58].

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 that 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

groups and longer durations when evaluating the role of medicinal plants for glaucoma therapy.

REFERENCES

1. Balunas MJ, Kinghorn AD. Drug discovery from medicinal plants. Life Sci. 2005;78(5):431-41. Epub 2005/10/04. doi: 10.1016/j.lfs.2005.09.012. PubMed PMID: 16198377.
2. Wyk B-Ev, Wink M. Medicinal plants of the world an illustrated scientific guide to important medicina plants and theier uses. Timber Press Inc. 2017.
3. Rhee DJ, Katz LJ, Spaeth GL, Myers JS. Complementary and alternative medicine for glaucoma. Surv Ophthalmol. 2001;46(1):43-55. Epub 2001/08/30. doi: 10.1016/s0039-6257(01)00233-8. PubMed PMID: 11525790.
4. Allingham RR, Damji KF, Shields MB. Shields textbook of glaucoma. 6th ed. Philadelphia: Wolters Kluwer Health/ Lippincott Williams & Wilkins; 2011. p. 433-7.
5. Yunard A, Oktariana VD, Artini W, Prihartono J. Comparison of Intraocular Pressure and Anterior Chamber Angle Changes between Pilocarpine and Laser Peripheral Iridotomy. J Curr Glaucoma Pract. 2019;13(1):32-6. Epub 2019/09/10. doi: 10.5005/jp-journals-10078-1245. PubMed PMID: 31496559.
6. Wilkinson JT, Fraunfelder FW. Use of herbal medicines and nutritional supplements in ocular disorders: an evidence-based review. Drugs. 2011;71(18):2421-34. Epub 2011/12/07. doi: 10.2165/11596840-000000000-00000. PubMed PMID: 22141385.
7. Tham YC, Li X, Wong TY, Quigley HA, Aung T, Cheng CY. Global prevalence of glaucoma and projections of glaucoma burden through 2040: a systematic review and meta-analysis. Ophthalmology. 2014;121(11):2081-90. Epub 2014/07/01. doi: 10.1016/j.ophtha.2014.05.013. PubMed PMID: 24974815.
8. Prum BE, Jr., Lim MC, Mansberger SL, Stein JD, Moroi SE, Gedde SJ, et al. Primary Open-Angle Glaucoma Suspect Preferred Practice Pattern((R)) Guidelines. Ophthalmology. 2016;123(1):P112-51. Epub 2015/11/20. doi: 10.1016/j.ophtha.2015.10.055. PubMed PMID: 26581560.
9. Binns CW, Lee MK, Lee AH. Problems and Prospects: Public Health Regulation of Dietary Supplements. Annu Rev Public Health. 2018;39:403-20. Epub 2017/12/23. doi: 10.1146/annurev-publhealth-040617-013638. PubMed PMID: 29272167.
10. Thomson P, Jones J, Browne M, Leslie SJ. Why people seek complementary and alternative medicine before conventional medical treatment: a population based study. Complement Ther Clin Pract. 2014;20(4):339-46. Epub 2014/08/27. doi: 10.1016/j.ctcp.2014.07.008. PubMed PMID: 25156988.
11. Wan MJ, Daniel S, Kassam F, Mutti G, Butty Z, Kasner O, et al. Survey of complementary and alternative medicine use in glaucoma patients. J Glaucoma. 2012;21(2):79-82. Epub 2010/12/22. doi: 10.1097/IJG.0b013e3182027c0c. PubMed PMID: 21173701.
12. Rhee DJ, Spaeth GL, Myers JS, Steinmann WC, Augsburger JJ, Shatz LJ, et al. Prevalence of the use of complementary and alternative medicine for glaucoma. Ophthalmology. 2002;109(3):438-43. Epub 2002/03/05. doi: 10.1016/s0161-6420(01)01030-2. PubMed PMID: 11874744.
13. Belyea DA, Alhabshan R, Del Rio-Gonzalez AM, Chadha N, Lamba T, Golshani C, et al. Marijuana Use Among Patients With Glaucoma in a City With Legalized Medical Marijuana Use. JAMA Ophthalmol. 2016;134(3):259-64. Epub 2016/01/01. doi: 10.1001/jamaophthalmol.2015.5209. PubMed PMID: 26719907.
14. Diamond BJ, Shiflett SC, Feiwel N, Matheis RJ, Noskin O, Richards JA, et al. Ginkgo biloba extract: mechanisms and clinical indications. Arch Phys Med Rehabil. 2000;81(5):668-78. Epub 2000/05/12. doi: 10.1016/s0003-9993(00)90052-2. PubMed PMID: 10807109.
15. de Souza Silva JE, Santos Souza CA, da Silva TB, Gomes IA, Brito Gde C, de Souza Araujo AA, et al. Use of herbal medicines by elderly patients: A systematic review. Arch Gerontol Geriatr. 2014;59(2):227-33. Epub 2014/07/27. doi: 10.1016/j.archger.2014.06.002. PubMed PMID: 25063588.
16. Gauthier AC, Liu J. Neurodegeneration and Neuroprotection in Glaucoma. Yale J Biol Med. 2016;89(1):73-9. Epub 2016/08/10. PubMed PMID: 27505018.
17. Goyal A, Srivastava A, Sihota R, Kaur J. Evaluation of oxidative stress markers in aqueous humor of primary open angle glaucoma and primary angle closure glaucoma patients. Curr Eye Res. 2014;39(8):823-9. Epub 2014/06/10. doi: 10.3109/02713683.2011.556299. PubMed PMID: 24912005.
18. Ferreira SM, Lerner SF, Brunzini R, Evelson PA, Llesuy SF. Oxidative stress markers in aqueous humor of glaucoma patients. Am J Ophthalmol. 2004;137(1):62-9. Epub 2004/01/01. doi: 10.1016/s0002-9394(03)00788-8. PubMed PMID: 14700645.
19. Mozaffarieh M, Grieshaber MC, Flammer J. Oxygen and blood flow: players in the pathogenesis of glaucoma. Mol Vis. 2008;14:224-33. Epub 2008/03/13. PubMed PMID: 18334938.
20. Nakazawa T, Nakazawa C, Matsubara A, Noda K, Hisatomi T, She H, et al. Tumor necrosis factor-alpha mediates oligodendrocyte death and delayed retinal ganglion cell loss in a mouse model of glaucoma. J Neurosci. 2006;26(49):12633-41. Epub 2006/12/08. doi: 10.1523/JNEUROSCI.2801-06.2006. PubMed PMID: 17151265.
21. Vecino E, Rodriguez FD, Ruzafa N, Pereiro X, Sharma SC. Glia-neuron interactions in the mammalian retina. Prog Retin Eye Res. 2016;51:1-40. Epub 2015/06/27. doi: 10.1016/j.preteyeres.2015.06.003. PubMed PMID: 26113209.
22. Wang K, Peng B, Lin B. Fractalkine receptor regulates microglial neurotoxicity in an experimental mouse glaucoma model. Glia. 2014;62(12):1943-54. Epub 2014/07/06. doi: 10.1002/glia.22715. PubMed PMID: 24989686.
23. Geyman LS, Suwan Y, Garg R, Field MG, Krawitz BD, Mo S, et al. Noninvasive Detection of Mitochondrial Dysfunction in Ocular Hypertension and Primary Open-angle Glaucoma. J Glaucoma. 2018;27(7):592-9. Epub 2018/05/12. doi: 10.1097/ijg.0000000000000980. PubMed PMID: 29750714.
24. Lascaratos G, Garway-Heath DF, Willoughby CE, Chau KY, Schapira AH. Mitochondrial dysfunction in glaucoma: understanding genetic influences. Mitochondrion.

2012;12(2):202-12. Epub 2011/12/06. doi: 10.1016/j.mito.2011.11.004. PubMed PMID: 22138560.
25. Mirzaei M, Gupta VB, Chick JM, Greco TM, Wu Y, Chitranshi N, et al. Age-related neurodegenerative disease associated pathways identified in retinal and vitreous proteome from human glaucoma eyes. Sci Rep. 2017;7(1):12685. Epub 2017/10/06. doi: 10.1038/s41598-017-12858-7. PubMed PMID: 28978942.
26. Eckert A, Keil U, Scherping I, Hauptmann S, Muller WE. Stabilization of mitochondrial membrane potential and improvement of neuronal energy metabolism by Ginkgo biloba extract EGb 761. Ann N Y Acad Sci. 2005;1056:474-85. Epub 2006/01/03. doi: 10.1196/annals.1352.023. PubMed PMID: 16387710.
27. Wu Y, Li S, Cui W, Zu X, Du J, Wang F. Ginkgo biloba extract improves coronary blood flow in healthy elderly adults: role of endothelium-dependent vasodilation. Phytomedicine. 2008;15(3):164-9. Epub 2008/02/09. doi: 10.1016/j.phymed.2007.12.002. PubMed PMID: 18258419.
28. Huang SY, Jeng C, Kao SC, Yu JJ, Liu DZ. Improved haemorrheological properties by Ginkgo biloba extract (Egb 761) in type 2 diabetes mellitus complicated with retinopathy. Clin Nutr. 2004;23(4):615-21. Epub 2004/08/07. doi: 10.1016/j.clnu.2003.10.010. PubMed PMID: 15297098.
29. Cybulska-Heinrich AK, Mozaffarieh M, Flammer J. Ginkgo biloba: an adjuvant therapy for progressive normal and high tension glaucoma. Mol Vis. 2012;18:390-402. Epub 2012/02/23. PubMed PMID: 22355250.
30. Quaranta L, Bettelli S, Uva MG, Semeraro F, Turano R, Gandolfo E. Effect of Ginkgo biloba extract on preexisting visual field damage in normal tension glaucoma. Ophthalmology. 2003;110(2):359-62; discussion 62-4. Epub 2003/02/13. doi: 10.1016/S0161-6420(02)01745-1. PubMed PMID: 12578781.
31. Guo X, Kong X, Huang R, Jin L, Ding X, He M, et al. Effect of Ginkgo biloba on visual field and contrast sensitivity in Chinese patients with normal tension glaucoma: a randomized, crossover clinical trial. Invest Ophthalmol Vis Sci. 2014;55(1):110-6. Epub 2013/11/28. doi: 10.1167/iovs.13-13168. PubMed PMID: 24282229.
32. Park JW, Kwon HJ, Chung WS, Kim CY, Seong GJ. Short-term effects of Ginkgo biloba extract on peripapillary retinal blood flow in normal tension glaucoma. Korean J Ophthalmol. 2011;25(5):323-8. Epub 2011/10/07. doi: 10.3341/kjo.2011.25.5.323. PubMed PMID: 21976939.
33. Sari MD, Sihotang AD, Lelo A. Ginkgo biloba extract effect on oxidative stress marker malonildialdehyde, redox enzyme gluthation peroxidase, visual field damage, and retinal nerve fiber layer thickness in primary open angle glaucoma. Int J Pharmtech Res. 2016;9:158-66.
34. DeKosky ST, Fitzpatrick A, Ives DG, Saxton J, Williamson J, Lopez OL, et al. The Ginkgo Evaluation of Memory (GEM) study: design and baseline data of a randomized trial of Ginkgo biloba extract in prevention of dementia. Contemp Clin Trials. 2006;27(3):238-53. Epub 2006/04/22. doi: 10.1016/j.cct.2006.02.007. PubMed PMID: 16627007.
35. DeKosky ST, Williamson JD, Fitzpatrick AL, Kronmal RA, Ives DG, Saxton JA, et al. Ginkgo biloba for prevention of dementia: a randomized controlled trial. JAMA. 2008;300(19):2253-62. Epub 2008/11/20. doi: 10.1001/jama.2008.683. PubMed PMID: 19017911.
36. Dodge HH, Zitzelberger T, Oken BS, Howieson D, Kaye J. A randomized placebo-controlled trial of Ginkgo biloba for the prevention of cognitive decline. Neurology. 2008;70(19 Pt 2):1809-17. Epub 2008/02/29. doi: 10.1212/01.wnl.0000303814.13509.db. PubMed PMID: 18305231.
37. West AL, Oren GA, Moroi SE. Evidence for the use of nutritional supplements and herbal medicines in common eye diseases. Am J Ophthalmol. 2006;141(1):157-66. Epub 2006/01/03. doi: 10.1016/j.ajo.2005.07.033. PubMed PMID: 16386992.
38. Gabor M. Pharmacologic effects of flavonoids on blood vessels. Angiologica. 1972;9(3-6):355-74. Epub 1972/01/01. doi: 10.1159/000157944. PubMed PMID: 4592457.
39. Head KA. Natural therapies for ocular disorders, part two: cataracts and glaucoma. Altern Med Rev. 2001;6(2):141-66. Epub 2001/04/17. PubMed PMID: 11302779.
40. Mian E, Curri SB, Lietti A, Bombardelli E. [Anthocyanosides and the walls of the microvessels: further aspects of the mechanism of action of their protective effect in syndromes due to abnormal capillary fragility]. Minerva Med. 1977;68(52):3565-81. Epub 1977/10/31. PubMed PMID: 593582.
41. Shim SH, Kim JM, Choi CY, Kim CY, Park KH. Ginkgo biloba extract and bilberry anthocyanins improve visual function in patients with normal tension glaucoma. J Med Food. 2012;15(9):818-23. Epub 2012/08/09. doi: 10.1089/jmf.2012.2241. PubMed PMID: 22870951.
42. Ohguro H, Ohguro I, Katai M, Tanaka S. Two-year randomized, placebo-controlled study of black currant anthocyanins on visual field in glaucoma. Ophthalmologica. 2012;228(1):26-35. Epub 2012/03/02. doi: 10.1159/000335961. PubMed PMID: 22377796.
43. Abuhasira R, Shbiro L, Landschaft Y. Medical use of cannabis and cannabinoids containing products - Regulations in Europe and North America. Eur J Intern Med. 2018;49:2-6. Epub 2018/01/14. doi: 10.1016/j.ejim.2018.01.001. PubMed PMID: 29329891.
44. National Conference of State Legislatures. State Medical Marijuana Laws [Internet]. 2019. Available from: http://www.ncsl.org/research/health/state-medical-marijuana-laws.aspx.
45. Zhan GL, Camras CB, Palmberg PF, Toris CB. Effects of marijuana on aqueous humor dynamics in a glaucoma patient. J Glaucoma. 2005;14(2):175-7. Epub 2005/03/03. doi: 10.1097/01.ijg.0000151882.07232.1d. PubMed PMID: 15741823.
46. Atakan Z. Cannabis, a complex plant: different compounds and different effects on individuals. Ther Adv Psychopharmacol. 2012;2(6):241-54. Epub 2013/08/29. doi: 10.1177/2045125312457586. PubMed PMID: 23983983.
47. Katz J, Costarides AP. Facts vs Fiction: the Role of Cannabinoids in the Treatment of Glaucoma. Current Ophthalmology Reports. 2019;7(3):177-81. doi: 10.1007/s40135-019-00214-z.
48. Hepler RS, Frank IR. Marihuana smoking and intraocular pressure. JAMA. 1971;217(10):1392. Epub 1971/09/06. PubMed PMID: 5109652.

49. Green K. Marijuana smoking vs cannabinoids for glaucoma therapy. Arch Ophthalmol. 1998;116(11):1433-7. Epub 1998/11/21. doi: 10.1001/archopht.116.11.1433. PubMed PMID: 9823341.
50. Sun X, Xu CS, Chadha N, Chen A, Liu J. Marijuana for Glaucoma: A Recipe for Disaster or Treatment? Yale J Biol Med. 2015;88(3):265-9. Epub 2015/09/05. PubMed PMID: 26339209.
51. Jay WM, Green K. Multiple-drop study of topically applied 1% delta 9-tetrahydrocannabinol in human eyes. Arch Ophthalmol. 1983;101(4):591-3. Epub 1983/04/01. doi: 10.1001/archopht.1983.01040010591012. PubMed PMID: 6301412.
52. Porcella A, Maxia C, Gessa GL, Pani L. The synthetic cannabinoid WIN55212-2 decreases the intraocular pressure in human glaucoma resistant to conventional therapies. Eur J Neurosci. 2001;13(2):409-12. Epub 2001/02/13. doi: 10.1046/j.0953-816x.2000.01401.x. PubMed PMID: 11168547.
53. Tiedeman JS, Shields MB, Weber PA, Crow JW, Cocchetto DM, Harris WA, et al. Effect of synthetic cannabinoids on elevated intraocular pressure. Ophthalmology. 1981;88(3):270-7. Epub 1981/03/01. doi: 10.1016/s0161-6420(81)35052-0. PubMed PMID: 7015221.
54. Miller S, Daily L, Leishman E, Bradshaw H, Straiker A. Delta9-Tetrahydrocannabinol and Cannabidiol Differentially Regulate Intraocular Pressure. Invest Ophthalmol Vis Sci. 2018;59(15):5904-11. Epub 2018/12/15. doi: 10.1167/iovs.18-24838. PubMed PMID: 30550613.
55. Tomida I, Azuara-Blanco A, House H, Flint M, Pertwee RG, Robson PJ. Effect of sublingual application of cannabinoids on intraocular pressure: a pilot study. J Glaucoma. 2006;15(5):349-53. Epub 2006/09/22. doi: 10.1097/01.ijg.0000212260.04488.60. PubMed PMID: 16988594.
56. Tomida I, Pertwee RG, Azuara-Blanco A. Cannabinoids and glaucoma. Br J Ophthalmol. 2004;88(5):708-13. Epub 2004/04/20. doi: 10.1136/bjo.2003.032250. PubMed PMID: 15090428.
57. Merritt JC, Crawford WJ, Alexander PC, Anduze AL, Gelbart SS. Effect of marihuana on intraocular and blood pressure in glaucoma. Ophthalmology. 1980;87(3):222-8. Epub 1980/03/01. doi: 10.1016/s0161-6420(80)35258-5. PubMed PMID: 7053160.
58. Novack GD. Cannabinoids for treatment of glaucoma. Curr Opin Ophthalmol. 2016;27(2):146-50. Epub 2016/02/04. doi: 10.1097/ICU.0000000000000242. PubMed PMID: 26840343.
59. Kwon YH, Fingert JH, Kuehn MH, Alward WL. Primary open-angle glaucoma. N Engl J Med. 2009;360(11):1113-24. Epub 2009/03/13. doi: 10.1056/NEJMra0804630. PubMed PMID: 19279343.
60. Shields MB. Normal-tension glaucoma: is it different from primary open-angle glaucoma? Curr Opin Ophthalmol. 2008;19(2):85-8. Epub 2008/02/28. doi: 10.1097/ICU.0b013e3282f3919b. PubMed PMID: 18301279.
61. Weinreb RN, Aung T, Medeiros FA. The pathophysiology and treatment of glaucoma: a review. JAMA. 2014;311(18):1901-11. Epub 2014/05/16. doi: 10.1001/jama.2014.3192. PubMed PMID: 24825645.
62. Lu LJ, Tsai JC, Liu J. Novel Pharmacologic Candidates for Treatment of Primary Open-Angle Glaucoma. Yale J Biol Med. 2017;90(1):111-8. Epub 2017/03/31. PubMed PMID: 28356898.
63. Allingham RR, Damji KF, Shields MB. Shields textbook of glaucoma. 6th ed. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2011. p. 390-9.
64. National Collaborating Centre for Acute Care (UK). Glaucoma: Diagnosis and Management of Chronic Open Angle Glaucoma and Ocular Hypertension. London: National Collaborating Centre for Acute Care (UK); 2009 Apr. PMID: 21938863.
65. Kuehn MH, Fingert JH, Kwon YH. Retinal ganglion cell death in glaucoma: mechanisms and neuroprotective strategies. Ophthalmol Clin North Am. 2005;18(3):383-95, vi. Epub 2005/08/02. doi: 10.1016/j.ohc.2005.04.002. PubMed PMID: 16054996.
66. Sena DF, Lindsley K. Neuroprotection for treatment of glaucoma in adults. Cochrane Database Syst Rev. 2017;1:CD006539. Epub 2017/01/26. doi: 10.1002/14651858.CD006539.pub4. PubMed PMID: 28122126.
67. Loskutova E, O'Brien C, Loskutov I, Loughman J. Nutritional supplementation in the treatment of glaucoma: A systematic review. Surv Ophthalmol. 2019;64(2):195-216. Epub 2018/10/09. doi: 10.1016/j.survophthal.2018.09.005. PubMed PMID: 30296451.