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REVIEW ARTICLE

Is the treatment of glaucoma limited to topical drops only?

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Abstract

Glaucoma is a degenerative condition characterized by progressive loss of retinal ganglion cells, leading to irreversible vision loss. This review aims to summarize the current knowledge about treatment strategies that optimize and improve glaucoma patients' outcomes. We explored various therapeutic options for glaucoma, highlighting the importance of methods beyond the traditional topical eye drops. We discussed the pharmacological options, as well as the more individualized treatment approaches e.g. surgical interventions and laser therapy. Moreover, we described the role of neuroprotection (e.g. antioxidants, anti-inflammatory agents, NMDAR inhibitors). Further research is needed to confirm the efficacy and safety of these neuroprotective agents. Regarding neovascular glaucoma, we focused on anti-VEGF agents and panretinal photocoagulation. Finally, we analyzed the potential adjunctive role of statins in the treatment of glaucoma. Although there is conflicting evidence regarding the efficacy of statins as a potential adjunctive glaucoma treatment, recent studies suggest possible benefits of this therapy.

Keywords: glaucoma · implants · neovascular · MIGS

Citation

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Abbreviations list

- AH – aqueous humor
- anti-VEGF – anti-vascular endothelial growth factor
- CAIs – carbonic anhydrase inhibitors
- CO2 – carbon dioxide
- DNA – deoxyribonucleic acid
- GDDs – glaucoma drainage devices
- HMG-CoA – β-hydroxy-β-methylglutaryl coenzyme A
- IOP – intraocular pressure
- LPI – laser peripheral iridotomy
- MIGS – minimally invasive glaucoma surgery
- MP-TSCPC – micropulsetransscleralcyclophotocoagulation
- NMDAR– N-methyl-D-aspartic acid receptors
- NPGS – non-penetrating glaucoma surgery
- NOS – nitric oxide synthase
- NVG – neovascular glaucoma
- OAG – open-angle glaucoma
- POAG – primary open-angle glaucoma
- PGAs – prostaglandins agents
- ROS – reactive oxygen species
- SLT – Selective laser trabeculoplasty
- THC – tetrahydrocannabinol
- Δ^8-THC – Δ-8-tetrahydrocannabinol
- Δ^9-THC – Δ-9-tetrahydrocannabinol
- TPLI – thermal laser peripheral iridoplasty

Introduction

Topical eye drops, as well as surgery and laser treatment, are the only proven methods of lowering the intraocular pressure, which is the best-known modifiable risk factor for the development of glaucoma [1-2]. The essence of this neuropathy is degeneration and progressive loss of retinal ganglion cells, resulting in the optic nerve changes [1]. Therefore, various therapeutic options that seem promising in preventing or slowing down the degenerative process and saving the function of the optic nerve should be considered. Hence, our review focuses on methods such as neuroprotection including reduction of oxidative stress, neuroinflammation and excitotoxicity (increased level of intracellular calcium, resulting in the damage of the plasma membrane, cytoskeleton, DNA and other cellular components), as well as the controversial use of statins or vascular medications in neovascular glaucoma. Our goal was to select articles that describe glaucoma treatment and summarize them in terms that non-ophthalmologists can understand, to expand their knowledge and help them provide the best care for their patients.

Material and methods

We searched the Medline database for articles published from 2010 to February 2024 in English and Polish. The chosen articles show both basic, advanced, and new methods of glaucoma treatment. The inclusion criteria were: full-text article, on-topic (glaucoma treatment). Case reports and letters to the Editor were excluded from the review.

Results

Drops, oral drugs and bimatoprost implant

Despite the development of numerous therapeutic options, it is impossible to discuss glaucoma treatment without mentioning the first-line therapy: topical eye drops. Six groups of drugs are available in the form of eye drops: prostaglandin agents, beta-blockers, carbonic anhydrase inhibitors, α2-mimetics, rho-kinase inhibitors and cholinomimetics [3]. If monotherapy with eye drops is insufficient to lower the intraocular pressure (IOP), switching to medication from another group should be considered before prescribing an additional topical drug [4-5] (see Figure 1). There is no equal target IOP for all patients, so it should be determined individually. The factors that facilitate setting the target IOP are glaucoma stage, age, life expectancy, value of IOP before the treatment, and glaucoma progression rate [6]. If the pace of vision loss is dynamic, the target IOP should be decreased. The elderly or patients with long life expectancies should have treatment aimed at lower IOP.

Carbonic anhydrase inhibitors (acetazolamide and the less commonly used methazolamide) are also available in pill form. They reduce the production of aqueous humor (AH) by inhibiting the transport of bicarbonates to the posterior chamber, which leads to decreased IOP levels [6]. Acetazolamide is prescribed to prevent the acute progression of glaucoma, for example in primary angle closure glaucoma or secondary glaucoma induced by the use of other medication (e.g. adrenergic agents, steroids, tramadol) [6-7]. The recommended dose of 250-1000 mg per day should be lowered in patients with renal impairment. Acetazolamide increases the elimination of bicarbonates in the urine, which can lead to metabolic acidosis. Patients with chronic lung diseases are more likely to develop metabolic acidosis, so before prescribing the drug, it is necessary to evaluate lung function (by examining arterial blood gas or pulmonary function tests) [6].

Hyperosmotic medications may also be useful in glaucoma therapy because their influence on intracellular fluid flow Decreases IOP. Intravenous mannitol is used as the last-line

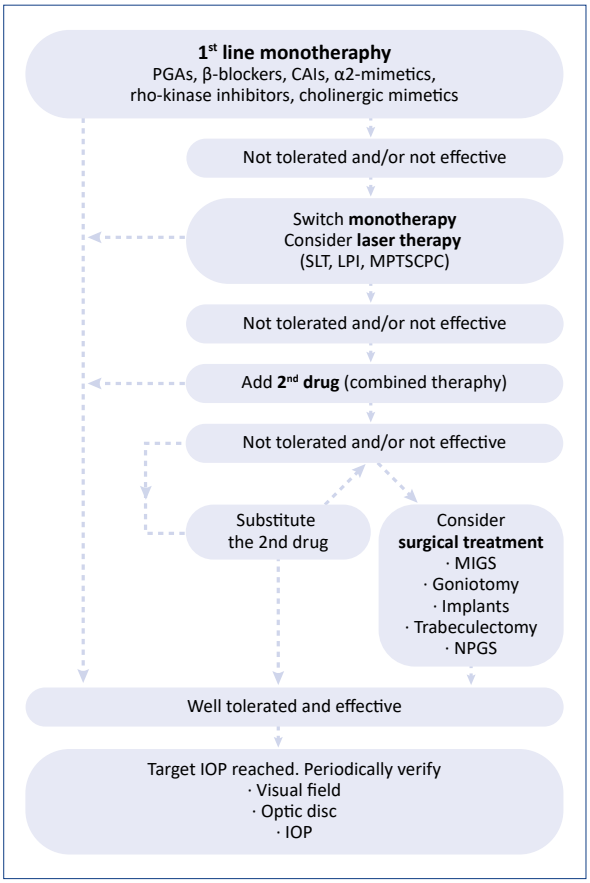

Figure 1. Suggested steps in the treatment of glaucoma

therapy [8]. Glycerol and isosorbide can be prescribed as oral drugs as well. Adverse effects of hyperosmotic medications include dehydration, increased diuresis and concentration of glucose, so they should be administered carefully to patients with diabetes mellitus [9]. Other adverse effects include nausea, vomiting, mental confusion and acute kidney insufficiency [5].

As implied by its name, the bimatoprost implant contains a prostaglandin analog. The implant is injected in the anterior chamber of the eye, where it constantly delivers bimatoprost to the ciliary body for about 3-4 months and acts more effectively than topical drops [10-12]. It is presumed that bimatoprost has a dual mechanism of action: reduces IOP by acting on the prostaglandin receptors in the trabecular meshwork which promotes the conventional outflow of AH and increases the outflow of AH through uveoscleral routes. Bimatoprost implants can be used in the treatment of open-angle glaucoma or ocular hypertension [10]. Due to decreased IOP, the complications of glaucoma (damage to the optic nerve and visual loss) are reduced [10]. The most common adverse reactions include irritation, pain, itching, watering of the eye and headache [13].

Laser therapy

The application of laser beam to the trabecular meshwork to improve AH outflow was introduced in 1972 [14]. Since then, improvements in laser technologies have led to their greater safety and effectiveness [15]. Currently, laser procedures target two main pathways of glaucoma treatment: decreasing AH production and increasing the aqueous outflow [16]. The European Glaucoma Society Guidelines recommend the following laser procedures: laser peripheral iridotomy (LPI), laser trabeculoplasty, thermal laser peripheral iridoplasty (TPLI) and cyclophotocoagulation [5].

Selective laser trabeculoplasty is the first choice in primary open-angle glaucoma. It is suggested that the therapeutic mechanism of SLT influences protein expression in the trabecular meshwork leading to increased AH outflow [17]. The most common indications of SLT include lack of compliance with treatment, anti-glaucomatous drops intolerance or pregnancy. Also, SLT is the appropriate approach in secondary open-angle glaucoma (e.g. pseudophakic glaucoma, pseudoexfoliation, pigmentary glaucoma) [15]. The Laser in Glaucoma and Ocular Hypertension Trial (LiGHT) has demonstrated the safety and effectiveness of SLT in glaucoma treatment, it can reduce the medication burden and potentially improve patients' quality of life [17-18].

LPI is recommended in primary angle closure glaucoma. The laser beam is used to create a full-thickness hole in the peripheral iris, in order to connect the anterior and posterior chambers and avoid the pupillary block [15]. LPI is the standard of care for acute primary angle closure glaucoma, which can potentially lead to blindness [19]. Also, LPI can be performed in the treatment of secondary angle closure glaucoma, where it lowers the IOP and prevents optic neuropathy. In addition, LPI can be done as a glaucoma prevention strategy, however such a decision needs precise clinical evaluation including the presence of risk factors (e.g. family history) [15].

Acute primary angle closure requires emergency intervention to immediately lower IOP and resolve the pupillary block. The strategies include medical treatment and laser peripheral iridotomy and primary lens extraction [20].

Laser peripheral iridoplasty applies low-energy laser burns to the peripheral iris to widen the anterior chamber angle. The expected outcome is immediate shrinkage of collagen and gradual contraction of a fibroblastic membrane, pulling the angle open mechanically. The procedure is applicable either as a stand-alone treatment for non-pupillary block angle closure or as an adjunctive therapy for pupillary block angle closure. Moreover, it has high effectiveness in treating reversible angle closure [15]. In cases when laser iridotomy is not effective in overcoming the pupillary block, surgical peripheral iridectomy is necessary.

Cyclodestructive techniques have been an available for the treatment of refractory glaucoma since the 1930s and their current version is micropulse transscleral cyclophotocoagulation (MP-TSCPC) [21]. Cyclophotocoagulation involves the destruction of the ciliary body structures (via damaging ciliary epithelium and blood vessels or coagulative necrosis) to decrease aqueous production and regain control of intraocular pressure. There are two approaches – external (transscleral) and internal (endoscopic) cyclophotocoagulation [15].

Surgical treatment

Although they are not first-line treatment, surgical procedures might be the only chance to preserve vision in patients with refractory glaucoma. When it comes to the progression of nerve cells' damage due to the glaucomatous process, patients might even be unaware of the advancement of the disease and because of that, they are often referred to surgical treatment too late. Several surgical techniques (e.g. trabeculectomy and its modifications) have been widely in use for years and some are getting more popular now due to less invasive procedures which are referred to as minimally invasive glaucoma surgery (MIGS) [5, 22].

MIGS may be considered in patients with primary open-angle glaucoma (POAG), pigmentary glaucoma and pseudoexfoliation glaucoma but also in cases of adverse drug reactions or non-compliance with treatment. Contraindications include primary and secondary angle-closure glaucoma, active neovascular glaucoma, corneal opacity, or angle dysgenesis [23]. MIGS procedures can be divided into the *ab interno* approach with a clear corneal incision that spares the conjunctiva and the *ab externo* approach, which refers to scleral or conjunctival incision [24-26]. *Ab interno* MIGS is considered safer due to the protection of the conjunctiva (allows uncomplicated operations if needed in the future) [27]. Devices used in MIGS can be assigned to the anatomical areas where their action is intended. Schlemm's canal targeted implants work by: bypassing the trabecular meshwork (which is presumed to be blocked in open-angle glaucoma), dilating the canal, removing a portion of the trabecular meshwork or by penetrating deep into the Schlemm's canal and trabecular meshwork, which creates a sclerotomy [22]. Suprachoroidal stent facilitates AH drainage by creating a patent lumen from the anterior chamber into the suprachoroidal space, which promotes AH outflow via the newly-formed pathway [27]. Subconjunctival shunts bypass the trabecular meshwork, create a new drainage pathway, or divert AH from the anterior chamber to the subconjunctival space [22]. MIGS procedures minimize tissue trauma, offer fewer complications than traditional surgical approaches and reduce the duration of postoperative care, therefore they are an attractive alternative to conventional surgery [28-30].

For decades, trabeculectomy was the most widely used surgical procedure in glaucoma treatment due to its well-established long-term efficacy [5, 31-32]. This form of treatment is recommended for patients in whom other forms of therapy have either failed or are not likely to achieve target IOP using medications or laser therapy at the very beginning. The procedure involves creating a flap in the sclera and is followed by partial removal of the trabecular meshwork and Schlemm's canal. If a piece of the iris is removed as well, the procedure is called iridectomy. Although a lot of changes in newer techniques (e.g. MIGS procedures, newer implants or shunts) have been introduced, among clinicians and patients there is a relatively high concern about complications [27, 33-34]. They can be so serious that reoperation may be needed [32]. For example filtering blebs scarring or leakage, aqueous misdirection (which is characterized by a shallow central and peripheral anterior chamber, displacement of the lens and normal or elevated IOP), bleb overfiltration with hypotony maculopathy, choroidal detachment, partial vision loss or even blindness [32-37].

A procedure with a similar name (trabeculotomy) that can be performed alone or as combined therapy with trabeculectomy [5]. It can be used in the surgical management of childhood glaucoma. Trabeculotomy lowers IOP via disruption of the Schlemm's canal and trabecular meshwork which facilitates the drainage of the aqueous humor. Its one main advantage is that it can be performed even if the cornea is cloudy (as in the case in childhood glaucoma). It is worth noticing that gonioscopy-assisted transluminal trabeculotomy is one of the trabecular-targeted MIGS techniques [30, 38-39].

Goniotomy is a procedure consisting of an incision of the trabeculum under the control of a gonioscopic lens. The main condition for performing goniotomy is that the cornea needs to be clear. Goniotomy is one of several methods used in primary congenital glaucoma treatment [40-41].

Implantation of glaucoma drainage devices (GDD) is indicated particularly for more severe cases or in the pediatric population. In adults, indications include excessive conjunctival scarring that diminishes the success of re-operations, abnormalities of the iridocorneal angle, neovascular glaucoma or presence of corneal grafts [42]. In children, GDDs are primarily used as reoperation after failed goniotomy or trabeculotomy and rarely as a first-line treatment in high-risk cases (e.g. aniridia, phakomatosis or aphakic glaucoma) [43]. GDDs were designed to overcome two problems with the trabeculectomy – to prevent the closure of the fistula diverting AH from the anterior chamber to the subconjunctival space (that is done with a silicone tube inserted into the anterior chamber and extended to the equatorial region of the eye) and to prevent failure of a filtering bleb because of conjunctival scarring to the sclera (this is done with an external plate that maintains potential space with a material that the conjuncti-

va cannot scar to and allows the creation of a capsule which is permeable for AH). There are non-valved implants such as Molteno or Baerveldt implants and valved implants such as Ahmed implants. Both types of implants (valved and non-valved) show significant IOP reduction, however the Ahmed implant (valved) reduces IOP less effectively, causing a greater need for glaucoma medications and a higher failure rate than the Baerveldt implant (non-valved) [44-47]. To decrease the risk of complications new GDDs are developed, e.g. the Paul Glaucoma Implant [28, 48-49].

The non-penetrating glaucoma surgery (NPGS) includes viscocanalostomy, canaloplasty, CO2 laser-assisted sclerectomy surgery and deep sclerectomy. These alternatives to traditional surgical procedures cause fewer complications, albeit they are demanding and the outcome depends on the operator's skills [50]. Deep sclerectomy is a relatively widely used NPGS method [51]. It involves removing the juxtacanalicular trabecula and the endothelium of Schlemm's canal (both have high resistance to AH outflow) with preservation of the thin trabeculo-Descement's membrane which allows permeating of AH [51-53]. Thereafter, AH can accumulate in a space within the sclera and eventually be drained through the subconjunctival space [53]. As a result, deep sclerotomy is an effective IOP-reducing operation for patients with open-angle glaucoma and can also be a treatment option for primary congenital glaucoma [51, 54].

Neuroprotection

Among various factors that significantly contribute to the pathogenesis of glaucoma, the role of oxidative stress, neuroinflammation and excitotoxicity is increasingly emphasized [55-56]. The excess of reactive oxygen species (ROS) damages the DNA, proteins, and lipids [57]. Research has shown that blood and aqueous humor levels of oxidative stress-related molecular biomarkers are greatly higher in samples taken from patients with developed glaucoma in comparison to healthy individuals [55, 58]. Inflammatory status is significantly changed as well. Dynamically elevating levels of various cytokines are observed [55, 59]. The use of substances with antioxidant and anti-inflammatory properties seems to be a reasonable solution for supporting glaucoma therapy. However, any therapeutic agents have not been explicitly approved for neuroprotection in glaucoma patients yet [8]. Many studies point to the antioxidant, anti-inflammatory and anti-apoptotic properties of *Ginkgo biloba*, *Lycium barbarum*, *Diospyros kaki*, *Tripterygium wilfordii*, saffron, curcumin, ginger, citicoline, caffeine, anthocyanin, coenzyme Q10, vitamins B3, D, E [55, 57, 60]. The results are conflicting on whether these substances have a clinically significant effect [57, 61]. Baicalein, forskolin, marijuana, ginsenoside, resveratrol and hesperidin are the other numerous natural substances, whose specific capability for lowering the intraocular pressure has been verified [55].

The use of marijuana for medical purposes including glaucoma treatment, is both interesting and controversial. In the 1970s-1980s of the XX century a number of studies were carried out to prove that the main psychoactive ingredient of cannabis, Δ-9-tetrahydrocannabinol (Δ^9-THC, commonly known as THC) is responsible for the IOP-lowering effect. Regardless of the route of THC administration (oral, intravenous, inhalation), a decrease in IOP was observed among people with and without glaucoma. Other classic cannabinoids (e.g. nabilone, Δ-8-tetrahydrocannabinol (Δ^8-THC), cannabinol, cannabidiol) and some THC metabolites have a similar effect on IOP [62-65]. Marijuana inhalation caused a reduction in IOP of patients with glaucoma within 30 minutes of administration and this effect lasted for approximately 4 hours [55]. Moreover, antioxidant and neuroprotective properties of cannabinoids have been reported [62]. In contrast, other studies describe the neurotoxicity of cannabis. They suggest that THC use is associated with increased neuronal background noise in the retina which leads to the altered neurotransmitter release [64, 66].

Marijuana's cardiovascular and neurological effects are also observed and may theoretically reduce the beneficial effect of lowering IOP by reducing ocular blood flow. The analyzed literature presents many disadvantages of cannabinoid use: very short duration of action, lack of evidence of a beneficial effect on the course of glaucoma, adverse effects (systemic and psychotropic) and the addiction potential. Current literature is consistent that evidence-based medicine does not explicitly recommend cannabis in any form of glaucoma treatment [66].

Hyperactivity of N-methyl-D-aspartic acid receptors (NMDAR) leads to the increased level of intracellular calcium, resulting in the damage of the plasma membrane, cytoskeleton, DNA and other cellular components. This process (referred to as excitotoxicity) affects the retinal ganglion cells, causing pathological changes co-responsible for the development of glaucoma [55-57]. Following that direction, NMDAR inhibitors and calcium channel blockers could potentially delay glaucoma progression, however this assumption has not been confirmed in randomized controlled trials among glaucoma patients, studying the utility of memantine (an NMDAR blocker commonly prescribed in Alzheimer's disease) [57, 67-68]. Nevertheless, in a placebo-controlled study on nilvadipine administered to patients with POAG for 3 years, Koseki et al. reported slowed visual field progression [69].

Wan et al. surveyed more than 1500 Canadian patients diagnosed with glaucoma and reported that almost 11% of them applied complementary and alternative medicine methods [70]. It should be clearly emphasized that reliable

research is necessary to determine the effects and safety of using those substances for medical purposes.

Vascular medications – neovascular glaucoma

Neovascular glaucoma (NVG), a type of secondary angle-closure glaucoma, characterized by intraocular neovascularization of the iris and/or anterior chamber angle, as well as increased IOP. Any disorder related to retinal ischemia (e.g. retinal venous obstructive disease, diabetic retinopathy, carotid artery obstructive disease, central retinal artery obstruction, ocular ischemic syndrome, rhegmatogenous retinal detachment, uveitis) may cause NVG [71]. The prolonged and intensified neovascularization and myofibroblast activity leads to the peripheral anterior synechiae and disruption of AH filtration, increasing IOP and a risk of glaucoma development. Panretinal photocoagulation is considered the gold standard therapy for pathological changes of the NVG. Positive effects of that procedure have been reported in many studies [71-73]. Alternatively to laser therapy, locally increased amounts of proteins involved in the neovascularization process might become a target for the NVG treatment. Therapy using anti-VEGF agents is being considered [71]. Studies on animal models document a rapid decrease in the intensity of anterior chamber neovascularization after the intravitreal injections of anti-VEGF antibodies: bevacizumab and ranibizumab [72, 74]. Unfortunately, these molecules do not have a high binding affinity to all VEGF isoforms and in consequence they are not an effective long-term solution. Aflibercept binds and influences multiple vascular growth factor isoforms, has a strong and long-standing biological effect [75]. A prospective case series revealed a rapid regression of early stages of iris and angle neovascularization in all included patients after an aflibercept injection [76]. Unfortunately, no guidelines for using intravitreal injections of anti-VEGF agents have been published, thus they remain as off-label methods [71]. A combined therapy based on the anti-VEGF proteins and the panretinal photocoagulation may be a treatment option [71]. A preoperative intravitreal injection with bevacizumab may reduce the risk of bleeding, inflammation and fibrosis after a trabeculectomy [77]. The same procedure resulted in greater IOP reduction and decreased incidence of complications after the GDD surgery [78]. Researchers wonder if a modification of ocular blood flow might play any role in effective glaucoma therapy [67]. A trial focused on dronabinol (a synthetic THC agent) investigated whether its oral administration affects the retinal vessel diameter, retinal oxygen saturation and retinal blood velocity, although the data have not been published yet [79].

Statins

Statins are commonly prescribed to patients with hyperlipidemia, however, they are of interest in glaucoma prevention and therapy [80]. Statins show wide pleiotropic effects whose molecular basis has not been precisely described [81]. They protect the retinal ganglion cells, probably due to their part in the inhibition of isoprenylation process, immunomodulation and decrease in the amount of glutamate [82]. Moreover, they activate the endothelial NOS and as a result, the retinal and choroidal blood flow improves, which results in a decreased IOP. Regulation of myosin II ATPase activity leads to a streamlined aqueous humor outflow in the iridocorneal angle [83].

Stein et al. reported a significant protective effect of 2 years of statin use. It is described as the 8% decreased risk of developing OAG in patients with hyperlipidemia treated with statins, compared to the individuals with hyperlipidemia who did not take them. The hypothesis is that statins inhibit glaucoma progression more effectively in the early stages of the disease.

A retrospective analysis of patients of the Erlanger Glaucoma Registry revealed that long-term treatment with statins, especially combined with acetylsalicylic acid correlated with a significantly reduced risk of glaucoma development and progression [84]. These results correspond to a prospective population-based cohort study done in the Netherlands which shows that long-term use (≥ 2 years) of statins results in reduced risk of OAG [85]. However, other studies did not confirm a significant relationship between statin use and the incidence and progression of glaucoma [81, 86]. That justifies further research to resolve this issue explicitly.

Conclusion

This review aimed to present current therapies for patients with glaucoma. It illustrates that the therapeutic choices in glaucoma go far beyond the well-known topical eye drops. What matters is that treatment must be individualized for every clinical patient, particularly taking into account the type of glaucoma and the patient's condition. Minimally invasive methods, GDD implants, laser and surgical therapies are commonly chosen solutions. We also pointed out less-known and controversial methods such as neuroprotection and the role of statins. The cited literature shows contradictory results whether these factors play any beneficial role in the glaucoma therapy. Nevertheless, some of the results were promising and justify further research on this topic.

Conflict of interest

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