Current situation and progress of drugs for reducing intraocular pressure

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Abstract: Glaucoma, the most common cause of irreversible blindness worldwide, usually causes characteristic optic nerve damage. Pathological intraocular pressure (IOP) elevation is a major risk factor. Drug reduction of IOP is the preferred treatment for clinicians because it can delay the progression of disease. However, the traditional IOP-lowering drugs currently used by patients may be poorly tolerated. Therefore, in recent years, some new drugs have been put into clinical application or in clinical phase I–III studies. They have a better IOP-lowering effect and fewer adverse reactions. Because glaucoma is a chronic disease, drugs need to be administered continuously for a long time. For patients, good compliance and high drug bioavailability have a positive effect on the prognosis of the disease. Therefore, clinicians and scientists have developed drug delivery systems to solve this complex problem. In addition, natural compounds and dietary supplements have a good effect of reducing IOP, and they can also protect the optic nerve through antioxidant action. We summarize the current traditional drugs, new drugs, sustained-release drug delivery systems, and complementary drugs and outline the mechanism of action and clinical effects of these drugs on glaucoma and their recent advances.

Keywords: drug delivery, drug treatment, glaucoma, intraocular pressure, natural product, neuroprotection

Introduction
Glucoma is an irreversible eye disease caused by the loss of retinal ganglion cells (RGCs). It is often associated with pathologically elevated intraocular pressure (IOP) and damage to the optic nerve. It is estimated that approximately 112 million people will be affected by glaucoma by 2040. In addition, glaucoma usually progresses without symptoms and is not detected until its advanced stages. As a result, this has a huge negative impact on the physical and mental health of patients, while posing a significant financial burden.

IOP is mainly maintained by the balance between the production and outflow of aqueous humor (AH). AH is secreted by the ciliary body, travels through the pupillary circulation to the anterior chamber, and then flows out through the conventional pathway of the trabecular meshwork (TM) and Schlemmer’s canal (SC) as well as the uveoscleral unconventional pathway. Moreover, IOP is the main modifiable risk factor. At present, the main ways to reduce IOP in clinical practice are by inhibiting the production rate of AH and promoting the outflow of AH from conventional or nonconventional routes. However, for glaucoma patients, the long-term administration of traditional eye drops may produce certain intolerance. Therefore, doctors and researchers have been looking for new targets for anti-glaucoma treatment.

Current modalities for lowering IOP mainly include medical therapy, laser therapy, and surgical therapy. Among them, drug therapy is the preferred treatment. However, it is still not sufficient for controlling the progression of the disease. Therefore, with the development of medical technology and the deepening of understanding of the pathogenesis of glaucoma, new anti-glaucoma drugs have emerged, providing ophthalmologists with a new choice.
The aim of this review is to discuss approaches to the pharmacological treatment of glaucoma, including with treatment with traditional drugs, new drugs, sustained-release drug delivery systems, and complementary medicines (Figure 1). With the emergence of new drugs and sustained-release drug delivery systems and complementary drugs, the drug treatment system for glaucoma will be greatly changed, which will bring a new direction to glaucoma patients.

**Traditional antiglaucoma drugs**

Currently, the traditional drugs used locally to reduce IOP mainly include cholinergic drugs, adrenergic agonists, carbonic anhydrase inhibitors (CAIs), beta-adrenoceptor antagonists, and prostaglandin (PG) (Table 1). The mechanisms of these drugs include the following: (1) inhibiting the production of AH in the ciliary body, (2) reducing the resistance of the TM outflow pathway, and (3) increasing AH drainage of a uveoscleral pathway.

### Table 1. Traditional medications for glaucoma.

| Drug class          | Mechanism of action                  | Adverse events                                                                 | Clinical application                                                                 | IOP reduction |
|---------------------|--------------------------------------|-------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|---------------|
| Cholinergic drugs   | Increasing AH outflow through the TM | Pupil narrowing, pseudomyopia, retinal detachment, night vision loss, headache, conjunctival hyperaemia; gastrointestinal disturbances, excessive salivation and sweating, slow heartbeat | A pre-treatment for laser glaucoma and in the treatment of acute angle-closure glaucoma. | 20–25%        |

(Continued)
Cholinergic drugs
Cholinergic drugs, the first class of drugs used to treat glaucoma, reduce IOP by increasing AH outflow through the TM. Major ocular adverse events include pupil narrowing, pseudomyopia, night vision loss, and conjunctival hyperemia. They may also cause adverse systemic reactions, such as gastrointestinal disturbances, headache, excessive salivation and sweating, and slow heart rate. Pilocarpine is currently most commonly used as a pre-treatment for laser glaucoma and in the treatment of acute angle-closure glaucoma.

Adrenergic agonists
The second class of IOP-lowering drugs are adrenergic agonists. They reduce IOP by a dual mechanism: reducing AH production and increasing uveoscleral outflow. At present, α-2 receptor agonists are mainly used in the clinic, among which brimonidine may have potential neuroprotective effects. The most significant local adverse reactions are allergic reactions, while the most common systemic reactions included dry mouth and central nervous system depression. Although brimonidine is not a first-line treatment for glaucoma, it can reduce IOP and control IOP for a short term with laser procedures.

Prostaglandins
Prostaglandins increase uveoscleral outflow and are at present, one of the most effective glaucoma drugs (with the largest IOP-lowering amplitude and the longest duration)
thoroughly. It has been shown in some reports that many drug-resistant patients have emerged. With the continuous development and application of new drugs today, the status of traditional drugs may be greatly impacted.

PGs
PGs are active metabolite products of arachidonic acid that regulate a large number of biological reactions in various tissues, including the eye.\textsuperscript{15,28} Prostaglandin receptor analogs (PGAs) for the treatment of glaucoma mainly cause ciliary muscle relaxation by binding to F-prostanoid (FP) and E-prostanoid (EP) receptors in the uveoscleral pathway, while disrupting the structure of the extracellular matrix (ECM) and inducing ECM remodeling in the ciliary muscle, iris root, and sclera, thereby reducing resistance to AH outflow and facilitating AH outflow.\textsuperscript{29} Some evidence suggests that PGAs also affect the traditional pressure-dependent pathway by causing cellular changes in the SC, but their effects are very minor. Their main adverse effect is a headache. For example, drugs such as latanoprost and travoprost have been widely used worldwide.

The cornerstone of contemporary glaucoma medicinal and surgical therapy is still IOP reduction. Modern drugs concentrate on controlling IOP by decreasing the production of AH or by enhancing outflow via the uveoscleral pathway. Less attention is given to other areas for IOP regulation, such as the TM, SC, collector channels, or episcleral venous system. Although parasympathomimetics may increase trabecular outflow, they also decrease uveoscleral outflow and frequently have systemic and ocular adverse effects, which restrict their usage.

According to the latest clinical guidelines for glaucoma, the five traditional drugs above are the first-line drugs for glaucoma treatment.\textsuperscript{30} PGs are currently the most commonly used and most effective drugs in clinical practice. Beta-adrenoceptor antagonists are also widely used in clinical practice and have extremely high safety and tolerability. The other three classes of drugs are also widely used in clinical practice, and appropriate drugs can be selected according to different types of glaucoma. Moreover, novel drugs have the potential to be used as the first-line drugs for glaucoma treatment. Adjuvant therapy mainly includes some antioxidants as well as plant drugs, which will be discussed later in this article.

**New topical drug therapy**

In recent years, in addition to the aforementioned classical glaucoma IOP-lowering drugs, some new drugs have also been put into clinical research or will be put into clinical application soon. Compared with the current traditional drugs, the new drugs have new clinical benefits and risks: although they can better reduce IOP and improve patient adherence, they may also bring new adverse reactions (Table 2).

| Drug (code name) | Mechanism of action | IOP-lowering mechanism | Clinical status | Disease or condition targeted | Manufacturer | IOP reduction |
|-----------------|---------------------|------------------------|----------------|-----------------------------|--------------|--------------|
| Netarsudil mesylate (AR-13324)\textsuperscript{31} | Rho kinase inhibitor | Increased conventional outflow | Launched-2018 | OHT OAG | Aerie Pharmaceuticals | From a baseline IOP of 22.5–22.6 mm Hg to 17.9–18.8 mm Hg |
| Latanoprostene Bunod (NCX-116)\textsuperscript{32} | NO donor | Increased conventional outflow | Launched-2017 | OHT OAG | Bausch & Lomb | IOP reductions of up to 9 mm Hg |
| NCX-470\textsuperscript{33} | NO donor | Increased conventional outflow | NCT04445519 (phase III) | OHT OAG | NicOx | −7.2 ± 2.8 mm Hg in 10HT-rabbits, −5.4 ± 0.7 mm Hg in ONT-dogs, −7.7 ± 1.4 mm Hg in OHT-monkeys |

(Continued)
### Table 2. (Continued)

| Drug (code name) | Mechanism of action | IOP-lowering mechanism | Clinical status | Disease or condition targeted | Manufacturer | IOP reduction |
|------------------|----------------------|------------------------|-----------------|-------------------------------|--------------|--------------|
| Omidenepeg Isopropyl (DE-117)34 | Prostaglandin EP2 agonist | Increased uveoscleral outflow | NCT03691662 (launched in Japan phase III in the USA) | Glaucoma OHT | Santen | At week 6 ranged from −7.11 ± 0.45 to −7.25 ± 0.49 mm Hg (−28.66 ± 1.80% to −29.17 ± 1.87%) in the BID arm |
| Omidenepeg (hDE-117)35 | Prostaglandin EP2 agonist | Increased uveoscleral outflow | Phase II study is unavailable | Glaucoma OHT | Santen | The mean IOP decreased by 2.5 ± 3.2 mm Hg in the POAG |
| Sepetaprost (DE-126)36 | Prostaglandin EP3 and F2α-agonist | Increased uveoscleral outflow | NCT04742283 (phase II) | Glaucoma OHT | Ono | The 4-h IOP reduction of 0.003% and 0.01% SPT were 16.2 ± 1.9%, and 16.4 ± 2.1%, respectively |
| FM10137 | ADORA3 modulator | Increased conventional outflow and Decreased AH production | NCT04585100 (phase II) | Glaucoma OHT | Future Medicine | It was comparable to the IOP-lowering effect of Xalatan |
| Bamosiran [SYL-040012]38 | ADRB2 expression inhibitor | Decreased AH production | NCT01739244 (phase II) | OHT | Sylentis | All compounds caused an IOP decrease of 20–35% |
| TAK-63939 | C-type natriuretic peptide analog | Increased conventional outflow and decreased AH production | NCT03131167 (phase II) | Glaucoma | Shire | IOP reduction ranging from 8.90% to 34.4% in the rabbit, from 16.5% to 26.4% in the dog, and from 3.43% to 13.5% in the monkey |
| LX-710140 | LIM Domain Kinase 1 (LIMK1) Inhibitor | Increased conventional outflow | NCT01528111 (phase II) | Glaucoma OHT | Lexicon Pharmaceuticals | The effect and the duration of action were similar as timolol |

**Rho kinase inhibitors**

Rho kinase inhibitors, one of the new glaucoma-targeted drugs, are also known as ROCK inhibitors, and they have IOP-lowering and some optic neuroprotective effects. They are an enzyme that promotes the contraction of TM cells, vascular endothelium, and other cells. Thus, they can relax TM smooth muscle to promote AH circulation in the TM pathway.

Netarsudil mesylate (AR-13324) is a Rho kinase inhibitor representative drug that is primarily used for the treatment of ocular hypertension (OHT) and open-angle glaucoma (OAG) and is administered as a single drop into the affected eye every night. In addition to the mechanism of Rho kinase inhibition, a clinical study highlighted the effect of netarsudil on the norepinephrine transporter (NET), and the pharmacological effect of NET inhibition is twofold: norepinephrine acts on the ciliary vessels to constrict them reducing AH formation, and norepinephrine continues to act on the norepinephrine receptors and increases the time course of IOP reduction.
Kahook et al.\textsuperscript{45} conducted a 12-month ROCKET-2 clinical trial and all reduced IOP above 17 mm Hg and maintained a stable IOP reduction, with adverse effects such as conjunctival congestion, corneal verticillata, and conjunctival hemorrhage. Moreover, a pooled analysis of ROCKET phases I–IV and a comparison with timolol drugs concluded that netarsudil had a highly effective IOP-lowering effect and tolerable adverse effects.

### Nitric oxide (NO) donors

NO is a small molecule gas signaling molecule mediating endothelial cell relaxation.\textsuperscript{46} NO lowers IOP by inducing relaxation of the TM and Schlemm’s canal (SC) through NO/sGC/cGMP and other pathways, increasing SC endothelial cell permeability and TM cell relaxation, thereby promoting the outflow of AH.\textsuperscript{47-49} There are many NO donors, including classical NO donors alone and combined NO donors, which have not only high efficacy in lowering IOP but also have synergistic effects in lowering IOP with combined therapy.\textsuperscript{49} Latanoprostene bunod (BOL-303259-X or NCX-116), a representative drug of the NO donor class.

In a phase III clinical study, patients with OAG and OHT were treated with a double mask for 3 months. Compared with timolol maleate, the IOP-lowering effect of latanoprostene bunod was superior.\textsuperscript{32} In other clinical studies, the use of latanoprostene bunod was ordered nightly in the latanoprostene bunod group and once daily in the morning and evening in the timolol maleate group, finally concluding that latanoprostene bunod was conclude to have a superior effect in lowering IOP at any time of the day, especially at night.\textsuperscript{50,51} In a recent retrospective study, changes in IOP in 56 patients using latanoprostene bunod since their visit and at various follow-up visits were reviewed, and 60% of patients had clinically significant IOP reduction. Latanoprostene bunod was found to be more tolerable to adverse effects and had superior IOP-lowering effects than conventional PGAs.\textsuperscript{52}

Ncx-470 is a novel NO donor class, a combination of a PG F2α agonist and an NO donor, also known as bimatoprost-NO, currently in clinical phase III. In a preclinical study, this class of drugs was demonstrated to possesses a powerful IOP-lowering effect in monkeys, rabbits, and dogs with OHT.\textsuperscript{33} In addition to NO having a therapeutic effect on glaucoma, NO donors have also made good progress.

### PG receptor agonists

PGAs are currently the most IOP-lowering drugs; thus, in addition to some traditional drugs, many emerging drugs are also undergoing clinical research. PGAs are mainly classified into FP agonists and EP2 receptor agonists according to their pharmacological characteristics. A representative new drug of EP2 receptor agonists is omidenepag isopropyl (DE-117), also known as OMDI, which is mainly used for the treatment of glaucoma and OHT.\textsuperscript{34} In a clinical phase II study comparing the therapeutic effect of OMDI once-versus twice-daily drops, the results showed that once-daily dosing was more effective.\textsuperscript{34} In a subsequent clinical phase III study, OMDI was compared with latanoprost in 190 patients for 1 month, and the results showed that OMDI was no less effective than latanoprost in lowering IOP, with a lower incidence of adverse effects and better tolerability.\textsuperscript{53} Omidenepag (hDE-117) is also a class of EP2 receptor agonists that is currently in phase II clinical studies. Some studies have shown that it is highly effective at lowering IOP in monkeys, making it a promising drug for glaucoma.\textsuperscript{35}

The FP agonist representative drug sepetaprost (DE-126) is a PG FP/EP3 receptor dual agonist in phase IIb clinical development. In a recent study comparing latanoprost with sepetaprost, a study was performed in mice, and the final results demonstrated that sepetaprost was no less effective than latanoprost and had a longer duration of action, possibly due to the increased AH efficacy of FP/EP3 receptor dual agonism.\textsuperscript{36} In its latest phase IIb study, a multicenter trial was conducted in the United States and Japan to explore the optimal concentration of sepetaprost and concluded that 0.002% sepetaprost was the optimal concentration.\textsuperscript{54} FP agonists titrated once daily are very effective in lowering IOP in glaucoma patients and controlling the diurnal variation of IOP. FP agonists have no systemic adverse events or local adverse events, with a high level of safety and efficacy.\textsuperscript{55}

PGAs were once shown to be the most IOP-lowering class of glaucoma drugs with the longest duration of action. With the application and
development of a variety of PGAs, it is promising to become one of the most mainstream drugs for glaucoma in the future.

**Adenosine receptor agonists**

There are four subtypes of adenosine receptors, A1, A2A, A2B and A3 receptors. Adenosine receptors are also present in many different ocular tissues, such as the retina, TM, and ciliary body. The main mechanism of adenosine receptor agonists is that adenosine is an important regulator of inflammation and fibrosis, which affects endogenous cell signaling by binding to multiple adenosine receptors and facilitating the digestion and degradation of TM collagen by proteases, thereby promoting AH outflow and lowering IOP.

To date, no adenosine receptor agonist for glaucoma treatment has been successfully approved by the US Food and Drug Administration (FDA). FM101 is an oral tablet of an A3 receptor modulator currently in a phase I/IIA trial (NCT04585100) whose primary mechanism of action is to have the effects of a β-arrestin antagonist and a G protein agonist. In a safety study of FM101, administered to rats over 28 days, adverse effects such as dilute stools, and ear flushing were observed, while its lethal dose should be greater than 2000 mg.

Trabodenoson (INO-8875) is an efficient class of adenosine A1 agonists that upregulates the activity of protein coenzyme A and MMP-2, promotes the degradation of type IV collagen fibers, alters the structure of TM cells. A study demonstrated the use of INO-8875 in adult and aged mice, and successfully demonstrated its significant IOP-lowering effect. Its role was also demonstrated in a phase II clinical trial (NCT01917383).

**Small interfering RNA (siRNA)**

Bamosiran (SYL-040012) is a siRNA for human-targeted adrenergic receptor (ADRB2) blocker that lowers IOP by inhibiting AH production in the ciliary body, and it is in the phase II clinical study. The first human phase I clinical trial on SYL040012 (NCT00990743) evaluated the safety, adverse effects, and other effects of the drug in 30 volunteers with IOP below 21 mm Hg. The effect of different doses of siRNA on IOP was observed. The drug was administered as eye drops into one eye, with the other eye serving as a control group. SYL040012 was safe and well tolerated for single and multiple doses, and it resulted in a significant reduction in overall IOP, with the IOP-lowering effect being more pronounced in patients with higher IOP. The follow-up phase II study (NCT01739244) showed that the 300µg/day dose significantly reduced IOP compared with the basal IOP values and the placebo group, and that patients using the three different doses of SYL040012 had good systemic tolerance and prognosis.

**C type natriuretic peptide analog**

TAK-639 (SHP-639) is a synthetic 9-amino acid C-type natriuretic peptide analog evaluated in Shire’s phase I clinical trial (NCT03131167) for the topical treatment of OHT or OAG. TAK-639 affects TM cells (GTM-3) via a cGMP signaling pathway, decreasing extrascleral venous pressure, increasing AH outflow and decreasing AH formation.

In an animal experiment, mice were subjected to various concentrations of the drug, which had a significant IOP-lowering effect. In another experiment, significant IOP-lowering effects of TAK-639 were demonstrated in dogs, monkeys, and rabbits. Furthermore, in plasma, TAK-639 was detectable only early after use and at low concentrations. In a follow-up phase I clinical trial, concentrations of 0.1%, 0.3%, and 0.6% TAK-639 were administered once daily to 63 subjects. The experimental results demonstrated that the 0.6% concentration had the most significant IOP-lowering effect, with ocular irritation sensation being its common adverse effect.

**LIM domain kinase inhibitors**

The main representative drug is LX-7101, a LIM domain kinase 1 (LIMK1) and LIM domain kinase 2 (LIMK2) and Rho kinase 2 (ROCK 2) inhibitor, developed by Lexicon Pharmaceuticals for the treatment of OAG and currently in phase I/II clinical studies. The mechanism of action of LIMK inhibitors is to promote the outflow of AH and thus reduce IOP by inducing the depolymerization of actin in TM. The main adverse effect is conjunctival congestion, and some studies have shown that inhibitors of LIMK produce fewer adverse effects than inhibitors of ROCK when used to lower IOP.
LIMK inhibitors can play an IOP-lowering role in glucocorticoid-treated mice. In its follow-up phase I/II clinical study (NCT01528111), it was found to exert some IOP-lowering effect in patients with OHT. This class of drugs is still in development, related studies are not sufficient, and further clinical exploration is urgently needed.

**Fixed-dose combinations (FDCs)**

Based on the three mainstream IOP-lowering approaches, drugs with different mechanisms of action interact and combine to produce mutual promotion while maximizing the therapeutic effect on patients. At the same time, compared with combinations of different individual drugs, FDCs can bring better compliance to patients.

Today, the FDCs used in major hospitals are brinzolamide/timolol, brimonidine/timolol, brinzolamide/brimonidine, latanoprost/timolol, and travoprost/timolol. Timolol appears most frequently in combination, followed by latanoprost. Novel FDCs, such as carteolol hydrochloride/latanoprost, netarsudil/latanoprost have been put into clinical use in recent years and has made good application progress. FDCs will occupy a larger proportion of future glaucoma treatments.

**Sustained-release drug delivery systems in glaucoma**

Drug therapy for glaucoma is based on the topical administration of drugs. After administering eye drops, reflex mechanisms such as blinking and tearing cause the drug to spill out, and the drug is rapidly cleared in the body because of the presence of physiological barriers, such as corneal epithelial cells and the blood-AH barrier, making the bioavailability of the drug less than 5%. Second, because most glaucoma patients need several IOP-lowering drugs to be ordered several times at the same time or in a single dose, adherence is low in many patients. More than 30% of glaucoma patients do not fully comply with medical advice, and more than 90% of patients have medication errors, resulting in progressive and severe vision loss due to unsatisfactory IOP control. Therefore, minimizing the number of doses and extending the duration of dosing can improve patient adherence and increase the bioavailability of ocular drug delivery. In recent years, the development and clinical application of sustained-release drug delivery systems, such as implants and inserts, which are very effective methods, have provided the possibility of solving the above problems (Table 3).

**Table 3. Sustained-release systems for glaucoma.**

| Sustained-release device | Implant site | Sustained-release drug | Manufacturer | Latest clinical trials | Clinical status | IOP reduction | Clinical indication |
|-------------------------|-------------|------------------------|--------------|------------------------|----------------|--------------|---------------------|
| The Bimatoprost ring   | Conjunctival fornices | Bimatoprost | ForSight VISION | NCT02742649 | Phase II | A mean reduction from baseline IOP of −3.2 to −6.4 mm Hg | OHT, OAG |
| Travoprost punctum plug (OTX-TP) | Puncta | Travoprost | Ocular Therapeutix | NCT04061044 | Phase III | The IOP reduction from baseline was 6.2 (23%), 5.4 (21%), and 7.5 mm Hg (28%) at 8 am, 10 am, and 4 pm, respectively | OHT, OAG |
| PPDS | Puncta | Latanoprost | Mati Therapeutics | NCT02014142 | Phase II | No exact data suggested | OHT, OAG |
| Bimatoprost sustained-release | Anterior chamber | Bimatoprost | Allergan | NCT02250651 | Phase III | At month 24, mean IOP reduction from baseline was 7.5, 7.3, 7.3, and 8.9 mm Hg in eyes treated with Bimatoprost SR 6, 10, 15, and 20 µg, respectively | OHT, OAG |

(Continued)
Table 3. (Continued)

| Sustained-release device | Implant site | Sustained-release drug | Manufacturer | Latest clinical trials | Clinical status | IOP reduction | Clinical indication |
|--------------------------|--------------|------------------------|--------------|------------------------|----------------|--------------|-------------------|
| ENV-S15<sup>70</sup>     | Anterior chamber | Travoprost | Envisia Therapeutics | NCT02371746 | Phase II | The treatment effect was maintained over 8 months with 35 ± 3% or 6.4 ± 0.6 mm Hg average decrease in IOP from a baseline of 18.6 ± 0.2 mm Hg | OHT, OAG |
| iDoes<sup>71</sup>       | Anterior chamber | Travoprost | Glaukos | NCT03868124 | Phase III | Mean IOP reduction from baseline was 7.4 or 7.8 mm Hg in 24 months | OHT, OAG |
| Latanoprost-elut-contact<sup>72</sup> | Cornea | Latanoprost | Harvard University | NCT04500574 | Phase I | The CLHI lowered IOP by 10.5 ± 1.4, 11.1 ± 4.0, and 10.0 ± 2.5 mm Hg on days 3, 5, and 8, respectively | OHT, OAG |

CLHI, high-dose contact lenses; IOP, intraocular pressure; NCT, National Clinical Trial; OAG, open-angle glaucoma; OHT, ocular hypertension; PPDS, Punctal Plug Delivery System; SR, Sustained-release.

**Topical bimatoprost ocular insert**

The topical bimatoprost ocular insert, also known as the bimatoprost ring, is in phase II clinical trials. It is an ocular ring composed of bimatoprost combined with a polypropylene structure placed between the superior and inferior conjunctival fornices.

Brant et al.<sup>66</sup> conducted a phase II study on the topical bimatoprost ocular insert and compared it with 0.5% timolol. The results showed that its IOP-lowering effect was not inferior, and the adverse effects of the two drugs were basically the same, with eye rings still present in 88.5% of patients after a 6-month course of treatment. The results of this study, although showing less effective IOP reduction than timolol, improved patient outcomes, and adherence and achieved a 20% reduction in pressure relative to baseline IOP. In a subsequent clinical study (NCT02742649), 55 patients were divided into four groups. The results of the study showed that the fixed combination had the most significant IOP-lowering effect, followed by bimatoprost ocular insert, and the main adverse effects were ocular discharge and conjunctival congestion.

**OTX-TP**

OTX-TP, consisting of polyethylene glycol (PEG) hydrogel and brimonidine polylactic acid (PLA), is a hydrogel puncta placed at the upper and lower punctas for the sustained-release of travoprost into the tear film on a continuous basis.<sup>73</sup> The drug is in phase III clinical development at Ocular Therapeuix. Preliminary studies have demonstrated that OTX-TP is well tolerated, with 100% retention over 10 days and a sustained IOP-lowering effect over 1 month.<sup>67</sup> Recently, a multicenter phase III clinical trial (NCT04061044) was completed. Another multicenter phase III clinical trial showed a significant reduction in IOP over a 12-month course, with a range of 3.27–5.72 mm Hg reduction relative to baseline IOP and more reduction in IOP at early time points.<sup>74</sup> OTX-TP continued to be well tolerated, with the main adverse effects being canaliculitis and lacrimal passage structural disorders, but their incidence was close to that of the placebo group.

**Latanoprost punctal plug delivery system (L-PPDS)**

The L-PPDS is also a punctal plug placed in the upper and lower punctas and comprises silicone-coated latanoprost. Its clinical phase II study (NCT02014142), which focused on evaluating its safety and IOP-lowering efficacy, showed a 5.7 mm Hg reduction in IOP relative to baseline after 4 weeks of treatment.<sup>68</sup> The main adverse effect was tearing.
Bimatoprost sustained-release

Bimatoprost sustained-release is an implant placed in the anterior chamber that releases bimatoprost slowly. Bimatoprost sustained-release showed good efficacy and safety over a period of up to 24 months, with a significantly stronger IOP-lowering effect than the topical group, and continued administration of sustained-release bimatoprost resulted in a reduction in long-term IOP.69 The results of a subsequent 20-month, multicenter, phase III clinical trial involving 528 patients showed that a 10 and 15µg bimatoprost implant was not inferior to 0.5% timolol in terms of IOP-lowering effects.75 The most common adverse effect was conjunctival congestion. Bimatoprost sustained-release met the target IOP and was effective at lowering IOP.

ENV515

ENV515 is a biodegradable sustained-release device containing a sustained-release formulation of travoprost and sterile nanoparticles, and an intraocular implant of ENV515 has been clinically tested in phase II for 6–12 months in the anterior chamber.73 In a phase II a nonclinical study, the device was implanted in the anterior chamber of beagle dogs for 8 months, with an IOP reduction of nearly 6.4 ± 0.6 mm Hg relative to baseline and a high safety and tolerability profile.70 In its follow-up study, a phase II clinical trial was conducted to recruit glaucoma patients with high-dose versus low-dose ENV515 and to compare it with 0.5% timolol maleate to assess 28-day efficacy after an observation period of nearly 12 months.76 The results showed that the low dose was well tolerated, and the high dose was able to reduce IOP by an additional 1.1 mm Hg with no serious adverse effects. The high dose showed greater potential in the treatment of glaucoma.

iDose

Another travoprost intraocular implant, iDose, which is injected into the anterior chamber, is also currently in development. This titanium implant is placed in the TM of the anterior chamber in the eye and is currently in a phase III clinical trial, with patient recruitment already completed. The results of 24 months in the phase IIb study showed that the mean IOP decreased by 7.4 or 7.8 mm Hg from baseline within the first 24 months in the immediate-release iDose group and the sustained-release iDose group, showing a noninferior effect.71

Latanoprost-elut contact lens

A contact lens (CL) is a viable sustained-release system whereby the drug is impregnated in the CL to induce diffusion to the tear film as well as the cornea, and the CL allows the drug to remain in the tear film for more than 30 minutes compared with a few minutes for topical eye drops. The bioavailability of the drug compared with topically applied eye drops can be improved, for example, by the addition of vitamin E to further improve the drug residence time.72 One study used latanoprost-elut contact lenses in glaucoma monkeys, where latanoprost was placed into a CL hydrogel to prepare two lenses of high versus low dose, and a latanoprost topical application control group.77 The results of the study showed that the effect of low-dose contact lenses (CL₄₀) was at least as effective as the topical use of latanoprost. The effect of CL₄₀ in lowering IOP was more stable. The safety and feasibility of CL₄₀ will be further explored in glaucoma patients with a placebo control group in its latest phase I clinical study (NCT04500574), which is expected to be completed in 2023. However, adherence to wearing CLs will be a great challenge.

Other drug delivery systems

Nanotechnology involves materials and devices smaller than 100 nm in size. Nanomedicine-based systems are also emerging technology in ophthalmic sustained-release systems, capable of sustained release of drugs or targeted gene therapy in different parts of the eye.78 Its main types of applications for glaucoma IOP-lowering therapy are through liposomes, nanoparticles, nanoparticles, and dendrimers,79,80 and it can deliver different glaucoma drugs, such as latanoprost, bevacinumab, timolol maleate, and mitomycin C. Most such applications are in preclinical studies and have shown excellent IOP-lowering properties in animal models of OHT.

Drug delivery systems against glaucoma are evolving, and different delivery systems also have their advantages and disadvantages. Noninvasive sustained-release drug delivery systems are the most convenient and safe for patients. iDose is one of the better outcomes because of its duration of action. At the same time, the
sustained-release administration mentioned in this article is based on IOP-lowering drugs, and these systems can also deliver neuroprotective effects with antiscarring glaucoma drugs to develop new treatments.

**Complementary or adjuvant therapeutic drugs**

In addition to the widely used or under investigation drugs for topical application in glaucoma and sustained-release drug delivery systems, complementary or adjuvant therapeutic drugs, such as dietary supplements or natural products, can also delay the disease progression of glaucoma and play a role in optic nerve protection and IOP reduction.\(^{81,82}\) They include supplements such as herbs, botanicals, and vitamins that have different mechanisms of action to counteract the progression of glaucoma and can be used as combination drugs or complementary therapies. An overview of these products is provided below (Table 4).

Cannabinoids have been used in the treatment of a variety of diseases, including neurological disorders, pain, and cancer, and more than 400 compounds have been isolated,\(^{83}\) of which the main ones used for medical treatment are \(\Delta^9\)-tetrahydrocannabinol (THC) and cannabidiol.

| Table 4. Complementary medications for glaucoma. |
|-----------------------------------------------|
| **Supplemental drug** | **Mechanism of action** | **Mode of administration** | **IOP reduction** | **Clinical indication** |
|------------------------|-------------------------|---------------------------|------------------|------------------------|
| Cannabinoid\(^{83}\)    | IOP reduction           | Oral, inhalation, sublingual, intravenous, topical | The maximum decrease of 6.6 ± 1.5 mm Hg occurred at 90 minutes | OHT, glaucoma          |
|                        | Anti-inflammation       |                           |                  |                        |
|                        | Antioxidant             |                           |                  |                        |
|                        | Non-steroidal           |                           |                  |                        |
| Forskolin\(^{84}\)     | IOP reduction           | Topical                   | Revealed a highly significant maximum reduction of 25% in IOP in 6 h | OHT, glaucoma          |
| Saffron\(^{85}\)       | Antioxidant             | Oral                      | Mean baseline IOP was 12.9 ± 3.7 decrease to 10.9 ± 3.3 mmHg | OHT, glaucoma          |
|                        | Anti-inflammation       |                           |                  |                        |
|                        | IOP reduction           |                           |                  |                        |
| Anthocyanins\(^{86}\)  | Antioxidant             | Oral                      | It decreases in IOP were observed at 2 weeks [1.89 ± 1.58 mmHg] and 4 weeks [1.19 ± 1.77 mmHg] from the baseline | OHT, glaucoma          |
|                        | IOP reduction           |                           |                  |                        |
|                        | Anti-inflammation       |                           |                  |                        |
| Hesperidin\(^{87}\)    | Antioxidant             | Oral                      | Significantly reduced the IOP level in dextrose induced ocular hypertension in rats | OHT, glaucoma          |
|                        | IOP reduction           |                           |                  |                        |
|                        | Anti-inflammation       |                           |                  |                        |
| Persimmon\(^{88}\)     | Antioxidant             | Oral                      | The mean IOP peak from 34.33 ± 6.53 mmHg in the microbeads group decreased to 21.33 ± 3.88 mm Hg in the EEDK (100 mg/kg) group | OHT, glaucoma          |
|                        | IOP reduction           |                           |                  |                        |
|                        | Anti-inflammation       |                           |                  |                        |
| Vitamin B3\(^{89}\)    | Mitochondria stabilization | Oral                      | It lessens the degree of IOP elevation | OHT, glaucoma          |
|                        | IOP reduction           |                           |                  |                        |
| Vitamin D\(^{90}\)     | IOP reduction           | Oral                      | The IOP gradually decreased by 20% in the ipsilateral eye and 15% or less in the contralateral eye after 7–8 h | OHT, glaucoma          |
| Cordyceps cicadae\(^{91}\) | Antioxidants           | Oral                      | It was also shown to alleviate 29.6% IOP at 0.2 mg/kg body weight in this rabbit model | OHT, glaucoma          |
|                        | Anti-inflammation       |                           |                  |                        |
|                        | IOP reduction           |                           |                  |                        |
| Resveratrol\(^{92}\)   | Antioxidant             | Oral, topical             | Reduction of IOP [5.5 ± 0.5 mmHg] in normotensive rabbits | OHT, glaucoma          |
|                        | Anti-inflammation       |                           |                  |                        |
|                        | IOP reduction           |                           |                  |                        |

EEDK, ethanol extract of persimmon leaves; IOP, intraocular pressure; OHT, ocular hypertension.
Cannabidiol (CBD). Cannabinoids have IOP-lowering effects and can be administered by different modes of IOP-lowering therapy, including oral, topical, and inhalation administration. However, when topical administration of this class of drugs is performed, the utilization of cannabinoids in the eye is not high due to their low solubility. The mechanism of its IOP-lowering effect is unclear, and some studies have shown that the maximum IOP-lowering effect occurs at approximately 1 h, with the lowering effect lasting only 3–4 h. Although cannabinoids have been legalized and approved for medical applications in some countries, they have not been clinically used for glaucoma due to their short duration of action and adverse effects.

Cordyceps cicadae (CC) is a Chinese herbal medicine with a long history. It is also known as the cicada flower, and it is a type of entomogenous fungus. It uses the larvae of the cicada as a medium to form a biological complex of worms and fungi. It has a variety of active components, such as polysaccharides, nucleosides, cordycepins, and N6-(2-hydroxyethyl) adenosine (HEA). Therefore, it has anti-inflammatory and antioxidant functions and IOP-lowering effects in glaucoma. Horng et al. applied Cordyceps cicadae mycelium (CCM) in a rat model of glaucoma and prepared hydrated and alcoholic extracts. After 4 weeks of intragastric administration, significant IOP-lowering effects were obtained. A recent study also concluded that CCM has a good IOP-lowering effect in rabbits and rats. In addition to animal models, clinical studies have also been carried out by Hsu et al. They recruited 46 patients with OHT and administered CCM capsules, which showed good IOP-lowering efficacy and could be used as an adjunct to functional foods.

In addition to CC, there are a variety of Chinese herbal medicines that also have similar utility. Forskolin is an extract of Coleus forskohlii and is mainly produced in India. It can affect AH production by regulating CAMP. A previous study showed that intra-arterial infusion of different concentrations of forskolin significantly reduced the rate of AH formation in isolated bovine eyes. The mechanism of decompression of forskolin was clearly described. In a subsequent clinical trial, eye drops prepared with 1% forskolin were used in glaucoma patients for 4 weeks, and they showed good IOP-lowering performance.

Saffron, the world’s most expensive aromatic medicinal plant, is called ‘gold spice’. Its pharmacological properties include anti-inflammatory, antioxidant, and antimicrobial properties. A randomized prospective trial showed that oral administration of 30 mg saffron daily significantly reduced IOP in patients with POAG after 3 weeks of treatment. Anthocyanins are pigments derived from a variety of fruits. They have many effects, such as antioxidant and neuroprotective properties. In one study, glaucoma patients were treated for 24 months with 50 mg anthocyanin daily supplementation and showed a reduction in IOP, and improved visual field progression. This supplement also improves blood flow around the optic nerve. Hesperidin is a flavanone regularly found in citrus fruits and is famous for its anti-inflammatory, antioxidant, and anticarcinogenic characteristics. In one animal model study, oral administration of hesperidin (25, 50, and 100 mg/kg) significantly reduced IOP levels in prednisolone acetate-treated OHT rats, showing promise in glaucoma treatment. Persimmon is a fruit rich in a variety of active substances and has antioxidant properties. The ethanol extract of persimmon leaves (EEDK) has antioxidant effects on flavonoids. One study demonstrated that EEDK controlled IOP by modulating soluble guanylate cyclase α-1, and showed considerable IOP-lowering effects in a mouse model of glaucoma.

Multivitamins have been shown to play IOP-lowering and protective roles in the development and progression of glaucoma, such as vitamins B and D. Vitamin B has several subtypes, and its efficacy for glaucoma treatment has also been demonstrated in several studies. In an early experiment using mice with OHT but without optic nerve degeneration, the neuroprotective effect of nicotinamide (vitamin B3) was confirmed, with 93% of the group with high doses of nicotinamide application eventually not developing glaucoma and reduced IOP at high doses. Vitamin D is also a popular research direction among glaucoma scholars, and its main mechanism is to lower IOP, which is achieved by increasing AH outflow from the TM pathway. In an early animal study, vitamin D administration was shown to regulate IOP in nonhuman primates, indicating that there is great scope for research on IOP regulation in humans. In addition, glaucoma patients or healthy people with vitamin D deficiency have higher IOP, showing the great
potential of the role of vitamin D in IOP control and regulation with its use in adjuvant therapy.

There is also a widely used complementary drug in animal models of glaucoma called resveratrol, a nontoxic chemical antioxidant found in grape skins, peanuts, and other plants. Several phase II clinical studies related to the treatment of neurodegenerative diseases have been conducted. Due to its potent antioxidant and anti-inflammatory functions, resveratrol has a broad therapeutic orientation and can provide optic neuroprotection and lower IOP in glaucoma treatment. Its IOP-lowering effect was confirmed in a study by Razali et al., where IOP reduction in a rat model of OHT was achieved by agonizing adenosine receptors and inhibiting the tumor growth factor (TGF)-β2 signaling pathway.

The above therapeutic drugs are also referred to as dietary supplements by the FDA, and none of these complementary drugs can be sold with an explicit indication of their therapeutic effect on glaucoma unless they have undergone multiple phases of clinical studies and have been registered with the FDA. These glaucoma supplements are also natural products, most of which have antioxidant and anti-inflammatory properties, and they are readily available and cost-effective. Although a series of experimental studies and clinical trials have shown that these drugs exhibit IOP-lowering or optic neuroprotective effects, they still cannot replace conventional glaucoma drugs for stand-alone treatment. They need to be tested repeatedly and pass approval before they can truly become part of adjuvant glaucoma treatment.

The effectiveness of a novel BDNF-targeting adeno-associated virus (AAV) gene therapy for glaucoma has been demonstrated in mouse models. By activating tropomyosin-related receptor kinase B, intravitreal injection of AAV2 vectors boosted BDNF synthesis and lengthened its half-life. In conclusion, gene therapy has made remarkable strides recently and has great promise for the treatment of glaucoma.

Discussion
Glaucoma is a multifactorial chronic disease, and IOP lowering remains the main modality of glaucoma treatment at present. Currently, the drug treatment of glaucoma is relatively mature, and traditional agents for lowering IOP focus on controlling IOP by reducing AH production or increasing outflow through the uveoscleral route. However, the main AH circulation pathway, the small beam network pathway, is neglected. Many novel drugs and drug sustained-release systems have been developed and combined with the adjuvant treatment of complementary drugs, but there are still a large number of challenges and development opportunities in clinical application and practice.

First, it is well known that the main approaches to reducing IOP include increasing the outflow of AH in two ways and reducing AH production and episcleral venous pressure. Under the guarantee of safety and effectiveness, drugs with strong efficacy and more mechanisms of action are expected to be used more in the future. At the same time, the treatment of glaucoma can be combined with different IOP-lowering mechanisms of action to maximize the therapeutic benefit.

Second, poor adherence will lead to further progression of glaucoma. There are many reasons for low patient adherence, including the lack of attention, poverty, other chronic diseases, and older age in terms of personal reasons at the same time. The reasons for the choice of dosing regimen include topical drugs used multiple times a
day and adverse drug reactions. For these reasons, the most effective way to address adherence involves fewer doses, a low incidence of adverse drug reactions, and improved patient self-awareness of medication; in particular, the sustained-release drug delivery system solves the main problem of patient compliance. At the same time, new topical drugs without preservatives will also further alleviate the problem of adverse reactions.

Moreover, the medication regimen for glaucoma patients will also change. Patients are generally treated with two or more combination drugs to control IOP levels and prevent disease progression. Traditional drug combinations include brimonidine and timolol as well as diuretics; with the marketing of new drugs in recent years, latanoprostene bunod, netarsudil, and their combination of topical drugs have achieved good efficacy. As a result, FDCs will occupy a major proportion and position in future glaucoma treatment and more stably control IOP through the synergistic effect of different drugs as well as multiple mechanisms.

Sustained-release drug delivery systems can also be used in combination on different implantation sites. With the rise of interdisciplinary disciplines, multifunctional biomaterials are also a major hotspot for the topical treatment of glaucoma in the future. Multilayer hydrogel balls effectively reduce IOP in animal models by sustained-release administration. A multifunctional anti-scarring platform (PVA@rGO-Ag/5-Fu) effectively reduced IOP by anti-fibrosis. They all use the special structure and performance of biomaterials to simultaneously contain therapeutic drugs, resulting in IOP-lowering effects.

In addition, natural products with complementary medications such as dietary supplements, will be part of glaucoma treatment. Multiple types of clinical studies and experimental studies have demonstrated its IOP-lowering effects. Meanwhile, FDA-recognized dietary supplements combined with local drugs, can also improve the adherence of patients to some extent. Whether they can become clinically used drugs in the future urgently needs further research progress.

**Conclusion**

Therefore, scientists have also developed potential therapeutic modalities, such as neuroprotection, gene therapy, and stem cell therapy. Taken together, with the continuous introduction of various types of drugs, including the current traditional drugs, new drugs, sustained-release drug delivery systems, and complementary drugs, the glaucoma drug treatment system will be more complete. Thus, the life of glaucoma patients can be improved, and the burden of glaucoma on patients and society can be reduced.

**Declarations**

**Ethics approval and consent to participate**

Not applicable.

**Consent for publication**

Not applicable.

**Author contributions**

**Peiyu Liu:** Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Writing – original draft; Writing – review & editing.

**Feifei Wang:** Conceptualization; Data curation; Investigation; Methodology; Writing – original draft.

**Yuning Song:** Formal analysis; Investigation; Validation.

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References
1. Russo R, Varano GP, Adornetto A, et al. Retinal ganglion cell death in glaucoma: exploring the role of neuroinflammation. Eur J Pharmacol 2016; 787: 134–142.
2. Jonas JB, Aung T, Bourne RR, et al. Glaucoma. Lancet 2017; 390.
3. Kang JM and Tanna AP. Glaucoma. Med Clin North Am 2021; 105: 493–510.
4. Dibas A and Yorio T. Glucocorticoid therapy and ocular hypertension. Eur J Pharmacol 2016; 787: 57–71.
5. Tham YC, Li X, Wong TY, et al. Global prevalence of glaucoma and projections of glaucoma burden through 2040. Ophthalmology 2014; 121: 2081–2090.
6. Stein JD, Khawaja AP and Weizer JS. Glaucoma in adults-screening, diagnosis, and management: a review. JAMA 2021; 325: 164–174.
7. Dirani M, Crowston JG, Taylor PS, et al. Economic impact of primary open-angle glaucoma in Australia. Clin Exp Ophthalmol 2011; 39: 623–632.
8. Szegedi S, Boltz A, Scharinger EM, et al. Quality of life in patients with glaucoma assessed by 39-item National Eye Institute Visual Functioning Questionnaire (NEI VFQ-39). Graefes Arch Clin Exp Ophthalmol 2021; 260: 1623–1631.
9. Weinreb RN, Aung T and Medeiros FA. The pathophysiology and treatment of glaucoma. JAMA 2014; 311: 1901–1911.
10. Storgaard L, Tran TL, Freiberg JC, et al. Glaucoma clinical research: trends in treatment strategies and drug development. Front Med 2021; 8: 733080.
11. Artero-Castro A, Rodriguez-Jimenez FJ, Jendelova P, et al. Glaucoma as a neurodegenerative disease caused by intrinsic vulnerability factors. Prog Neurobiol 2020; 193: 101817.
12. Kinney M, Johnson AD, Reddix M, et al. Temporal effects of 2% pilocarpine ophthalmic solution on human pupil size and accommodation. Mil Med 2020; 185: 435–442.
13. Öh DJ, Chen JL, Vajaranant TS, et al. Brimonidine tartrate for the treatment of glaucoma. Expert Opin Pharmacother 2019; 20: 115–122.
14. Mincione F, Scozzafava A and Supuran CT. The development of topically acting carbonic anhydrase inhibitors as antiglaucoma agents. Curr Pharm Des 2008; 14: 649–654.
15. Matsou A and Anastasopoulos E. Investigational drugs targeting prostaglandin receptors for the treatment of glaucoma. Expert Opin Investig Drugs 2018; 27: 777–785.
16. Skaat A, Rosman MS, Chien JL, et al. Effect of pilocarpine hydrochloride on the schlemm canal in healthy eyes and eyes with open-angle glaucoma. JAMA Ophthalmol 2016; 134: 976–981.
17. Realini T. A history of glaucoma pharmacology. Optom Vis Sci 2011; 88: 36–38.
18. Micah K, Johnson AD, Michael R, et al. Temporal effects of 2% pilocarpine ophthalmic solution on human pupil size and accommodation. Mil Med 2020; 185(Suppl. 1): 435–442.
19. Marchand DK and McCormack S. Pilocarpine for radiotherapy-induced dry mouth and dry eyes: a review of clinical effectiveness, cost-effectiveness, and guidelines. Ottawa, ON, Canada: Canadian Agency for Drugs and Technologies in Health, 2020.
20. Chan PP, Pang JC and Tham CC. Acute primary angle closure–treatment strategies, evidences and economical considerations. Eye 2019; 33: 110–119.
21. Reitsamer H, Posey M and Kiel J. Effects of a topical α2 adrenergic agonist on ciliary blood flow and aqueous production in rabbits. Exp Eye Res 2006; 82: 405–415.
22. Conti F, Romano GL, Eandi CM, et al. Brimonidine is neuroprotective in animal paradigm of retinal ganglion cell damage. Front Pharmacol 2021; 12: 705405.
23. Bowman RJ, Cope J and Nischal KK. Ocular and systemic side effects of brimonidine 0.2% eye drops (Alphagan) in children. Eye 2004; 18: 24–26.
24. Supuran CT, Altamimi ASA and Carta F. Carbonic anhydrase inhibition and the management of glaucoma: a literature and patent review 2013–2019. Expert Opin Ther Pat 2019; 29: 781–792.
25. Gulati S and Aref AA. Oral acetazolamide for intraocular pressure lowering: balancing efficacy and safety in ophthalmic practice. *Expert Rev Clin Pharmacol* 2021; 14: 955–961.

26. Frishman WH, Fukuimura MS and Tannenbaum M. Topical ophthalmic β-adrenergic blockade for the treatment of glaucoma and ocular hypertension. *J Clin Pharmacol* 1994; 34: 795–803.

27. Yoon DJ, Kaur R, Gallegos A, et al. Repurposing ophthalmologic timolol for dermatologic use: caveats and historical review of adverse events. *Am J Clin Dermatol* 2021; 22: 89–99.

28. Angeli A and Supuran CT. Prostaglandin receptor agonists as antiglaucoma agents (a patent review 2013–2018). *Expert Opin Ther Pat* 2019; 29: 793–803.

29. Aihara M. Prostanoid receptor agonists for glaucoma treatment. *Jpn J Ophthalmol* 2021; 65: 581–590.

30. Gedde SJ, Vinod K, Wright MM, et al. Primary open-angle glaucoma preferred practice pattern®. *Ophthalmology* 2021; 128: P71–P150.

31. Hoy SM. Netarsudil ophthalmic solution 0.02%: first global approval. *Drugs* 2018; 78: 389–396.

32. Weinreb RN, Liebmann JM, Martin KR, et al. Latanoprostene bunod 0.024% in subjects with open-angle glaucoma or ocular hypertension: pooled phase 3 study findings. *J Glaucoma* 2018; 27: 7.

33. Impagnatiello F, Toris CB, Batugo M, et al. Intraocular pressure–lowering activity of NCX 470, a novel nitric oxide–donating bimatoprost in preclinical models. *Invest Ophthalmol Vis Sci* 2015; 56: 6558–6564.

34. Olander KW, Sato MA, Abrams MA, et al. A randomized phase 2 trial comparing omeprazole and esomeprazole for primary open-angle glaucoma or ocular hypertension (SPECTRUM-6). *J Glaucoma* 2021; 30: 473.

35. Iwamura R, Tanaka M, Okanari E, et al. Identification of a selective, non-prostanoid EP2 receptor agonist for the treatment of glaucoma: omeprazole and its prodrug omeprazol isopropyl. *J Med Chem* 2018; 61: 6869–6891.

36. Yamagishi-Kimura R, Han CT, Sakaguchi Y, et al. Safety evaluation of FM101, an A3 adenosine receptor modulator, in rat, for developing as therapeutics of glaucoma and hepatisis. *EXCLI J* 2020; 19: 187–200.
50. Weinreb RN, Scassellati Sforzolini B, Vittitov J, et al. Latanoprostene bunod 0.024% versus timolol maleate 0.5% in subjects with open-angle glaucoma or ocular hypertension: the APOLLO study. *Ophthalmology* 2016; 123: 965–973.

51. Liu JHK, Slight JR, Vittitow JL, et al. Two-year experience with latanoprostene bunod in clinical practice. *J Glaucoma* 2021; 30: 776–780.

52. Radell JE, Sharma HK, Auyeung KL, et al. Adenosine receptors as promising targets for the management of ocular diseases. *Med Chem Res* 2016; 10: 757–764.

53. Impagnatiello F, Bastia E, Almirante N, et al. Prostaglandin analogues and nitric oxide contribution in the treatment of ocular hypertension and glaucoma. *Br J Pharmacol* 2019; 176: 1079–1089.

54. Spinozzi E, Baldassarri C, Acquaticci L, et al. Adenosine receptors as promising targets for the management of ocular diseases. *Med Chem Res* 2021; 30: 353–370.

55. Jacobson KA, Tosh DK, Jain S, et al. Historical and current adenosine receptor agonists in preclinical and clinical development. *Front Cell Neurosci* 2019; 13: 124.

56. Li G, Torrejon KY, Unser AM, et al. Trabodenoson, an adenosine mimic with A1 receptor selectivity lowers intraocular pressure by increasing conventional outflow facility in mice. *Invest Ophthalmol Vis Sci* 2018; 59: 383–392.

57. Moreno-Montañés J, Sádaba B, Ruz V, et al. Phase I clinical trial of SYL040012, a small interfering RNA targeting β-adrenergic receptor 2, for lowering intraocular pressure. *Mol Ther* 2014; 22: 226–232.

58. Li G, Torrejon KY, Unser AM, et al. Pharmacokinetics and intraocular pressure–lowering activity of TAK-639, a novel C-type natriuretic peptide analog, in rabbit, dog, and monkey. *Exp Eye Res* 2019; 189: 107836.

59. Martin P, Cohen A, Uddin S, et al. Randomized, double-masked, placebo-controlled dose escalation study of TAK-639 topical ophthalmic solution in subjects with ocular hypertension or primary open-angle glaucoma. *Clin Ophthalmol* 2020; 14: 885–896.
71. Kesav NP, Young CEC, Ertel MK, et al. Sustained-release drug delivery systems for the treatment of glaucoma. *Int J OphthalmoM 2021; 14: 148–159.

72. Ciolino JB, Ross AE, Tulsan R, et al. Latanoprost-eluting contact lenses in glaucomatous monkeys. *Ophthalmology 2016; 123: 2085–2092.

73. Kompella UB, Hartman RR and Patil MA. Extraocular, periocular, and intraocular routes for sustained drug delivery for glaucoma. *Prog Retin Eye Res 2021; 82: 100901.

74. Vantipalli S, Sall KN, Stein E, et al. Evaluation of the safety and efficacy of OTX-TP, an intracanalicular travoprost insert, for the treatment of patients with open-angle glaucoma or ocular hypertension: a phase 3 study. *Invest OphthalmoM Vis Sci 2020; 61: 3488.

75. Bacharach J, Tatham A, Ferguson G, et al. Phase 3, randomized, 20-month study of the efficacy and safety of bimatoprost implant in patients with open-angle glaucoma and ocular hypertension (ARTEMIS 2). *Drugs 2021; 81: 2017–2033.

76. Hsu KH, Fentzke RC and Chauhan A. Feasibility of corneal drug delivery of cysteamine using vitamin E modified silicone hydrogel contact lenses. *Eur J Pharm Biopharm 2013; 85(3 Pt. A): 531–540.

77. Zhai Z, Cheng Y and Hong J. Nanomedicines for the treatment of glaucoma: current status and future perspectives. *Acta Biomater 2021; 125: 41–56.

78. Schnichels S, Hurst J, de Vries JW, et al. Improved treatment options for glaucoma with brimonidine-loaded lipid DNA nanoparticles. *ACS Appl Mater Interfaces 2021; 13: 9445–9456.

79. Wang J, Li B, Huang D, et al. Nano-in-nano dendrimer gel particles for efficient topical delivery of antiglaucoma drugs into the eye. *Chem Eng J 2021; 425: 130498.

80. Ige M and Liu J. Focus: plant-based medicine and pharmacology: herbal medicines in glaucoma treatment. *Yale J Biol Med 2020; 93: 347.

81. Fahmideh F, Marchesi N, Barbieri A, et al. Non-drug interventions in glaucoma: putative roles for lifestyle, diet and nutritional supplements. *Surv OphthalmoM 2021; 67: 675–696.

82. Whiting PF, Wolff RF, Deshpande S, et al. Cannabinoids for medical use: a systematic review and meta-analysis. *JAMA 2015; 313: 2456–2473.

83. Majeeed M, Nagabhushanam K, Natarajan S, et al. A double-blind, randomized clinical trial to evaluate the efficacy and safety of forskolin eye drops 1% in the treatment of open angle glaucoma—a comparative study. *J Clin Trials 2014; 4: 184.

84. Jabbarpoor Bonayd MH, Yazdani S and Saadat S. The ocular hypotensive effect of saffron extract in primary open angle glaucoma: a pilot study. *BMC Complement Altern Med 2014; 14: 1–6.

85. Lu B, Wang X, Ren Z, et al. Anti-glaucoma potential of hesperidin in experimental glaucoma induced rats. *AMB Express 2020; 10: 1–6.

86. Ahn HR, Yang JW, Kim JY, et al. The intraocular pressure-lowering effect of persimmon leaves (Diospyros kaki) in a mouse model of glaucoma. *Int J Mol Sci 2019; 20: 5268.

87. Williams PA, Harder JM, Foxworth NE, et al. Vitamin B3 modulates mitochondrial vulnerability and prevents glaucoma in aged mice. *Science 2017; 355: 756–760.

88. Abouzeid H and Samer CF. Vitamin D and glaucoma: a critical review of the literature. *J OphthalmoM 2020; 2020: 1–8.

89. Lee LY, Hsu JH, Fu HI, et al. Lowering the intraocular pressure in rats and rabbits by cordyceps cicadae extract and its active compounds. *Molecules 2022; 27.

90. Garcia-Medina JJ, Rubio-Velazquez E, Lopez-Bernal MD, et al. Glaucoma and antioxidants: review and update. *Antioxidants 2020; 9: 1031.

91. Rafuse P and Buys YM. Medical use of cannabis for glaucoma. *Can J OphthalmoM 2019; 54: 7–8.

92. Merritt JC, Crawford WJ, Alexander PC, et al. Effect of marihuana on intraocular and blood pressure in glaucoma. *Ophthalmology 1980; 87: 222–228.

93. Merritt JC, Olsen JL, Armstrong JR, et al. Topical Δ9-tetrahydrocannabinol in hypertensive glaucomas. *J Pharm Pharmacol 1981; 33: 40–41.

94. Brown B, Adams AJ, Haegerstrom-Portnoy G, et al. Pupil size after use of marijuana and alcohol. *Am J OphthalmoM 1977; 83: 350–354.
97. Horng CT, Yang YL, Chen CC, et al. Intraocular pressure-lowering effect of Cordyceps cicadae mycelia extract in a glaucoma rat model. Int J Med Sci 2021; 18: 1007–1014.

98. Hsu J-H, Chang W-J, Fu H-I, et al. Clinical evaluation of the short-term effects of Cordyceps cicadae mycelium in lowering intraocular pressure. J Funct Foods 2022; 95: 105177.

99. Shahidullah M, Wilson WS, Rafiq K, et al. Terbutaline, forskolin and cAMP reduce secretion of aqueous humour in the isolated bovine eye. PLoS ONE 2020; 15: e244253.

100. Rasool A, Imran Mir M, Zulfajri M, et al. Plant growth promoting and antifungal asset of indigenous rhizobacteria secluded from saffron (Crocus sativus L.) rhizosphere. Microb Pathog 2021; 150: 104734.

101. Khoo HE, Azlan A, Tang ST, et al. Anthocyanidins and anthocyanins: colored pigments as food, pharmaceutical ingredients, and the potential health benefits. Food Nutr Res 2017; 61: 1361779.

102. Gandhi GR, Vasconcelos ABS, Wu D-T, et al. Citrus flavonoids as promising phytochemicals targeting diabetes and related complications: a systematic review of in vitro and in vivo studies. Nutrients 2020; 12: 2907.

103. Ryul Ahn H, Kim K-A, Kang SW, et al. Persimmon leaves (Diospyros kaki) extract protects optic nerve crush-induced retinal degeneration. Sci Rep 2017; 7: 1–10.

104. Kutuzova GD, B’Ann TG, Kiland JA, et al. 1α, 25-Dihydroxyvitamin D3 and its analog, 2-methylene-19-nor-(20S)-1α, 25-dihydroxyvitamin D3 (2MD), suppress intraocular pressure in non-human primates. Arch Biochem Biophys 2012; 518: 53–60.

105. Razali N, Agarwal R, Agarwal P, et al. IOP lowering effect of topical trans-resveratrol involves adenosine receptors and TGF-β2 signaling pathways. Eur J Pharmacol 2018; 838: 1–10.

106. Sim RH, Sirasanagandla SR, Das S, et al. Treatment of glaucoma with natural products and their mechanism of action: an update. Nutrients 2022; 14: 534.

107. Wilson AM and Di Polo A. Gene therapy for retinal ganglion cell neuroprotection in glaucoma. Gene Ther 2012; 19: 127–136.

108. Thomson BR, Liu P, Onay T, et al. Cellular crosstalk regulates the aqueous humor outflow pathway and provides new targets for glaucoma therapies. Nat Commun 2021; 12: 1–16.

109. Wu J, Bell OH, Copland DA, et al. Gene therapy for glaucoma by ciliary body aquaporin 1 disruption using CRISPR-Cas9. Mol Ther 2020; 28: 820–829.

110. Osborne A, Khatib TZ, Songra L, et al. Neuroprotection of retinal ganglion cells by a novel gene therapy construct that achieves sustained enhancement of brain-derived neurotrophic factor/tropomyosin-related kinase receptor-B signaling. Cell Death Dis 2018; 9: 1–18.

111. Imperato JS, Zou KH, Li JZ, et al. Clinical practice management of primary open-angle glaucoma in the United States: an analysis of real-world evidence. Patient Prefer Adherence 2022; 16: 2213–2227.

112. Ha A, Jang M, Shim SR, et al. Interventions for glaucoma medication adherence improvement: a network meta-analysis of randomized controlled trials. Ophthalmology 2022; 129: 1294–1304.

113. Wang F, Song Y, Huang J, et al. Lollipop-inspired multilayered drug delivery hydrogel for dual effective, long-term, and NIR-defined glaucoma treatment. Macromol Biosci 2021; 21: e2100202.

114. Wang Y, Xu Z, Li W, et al. A graphene-Ag based near-infrared defined accurate anti-scarring strategy for ocular glaucoma surgery. Biomaterials Sci 2022; 10: 1281–1291.