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Review TDD

A Review on Kaempferol Eye Drops for the Glaucoma Treatment

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Abstract

One of the main causes of permanent blindness, glaucoma is defined by gradual damage to the optic nerve, mostly brought on by oxidative stress, neuroinflammation, and high intraocular pressure (IOP). The investigation of herbal alternatives is necessary since current synthetic therapies, such as beta-blockers and prostaglandin analogs, frequently result in ocular discomfort, systemic toxicity, and poor patient compliance. Clitoria ternatea contains kaempferol, a bioactive flavonoid that has shown anti-inflammatory, antioxidant, and neuroprotective qualities, making it a viable option for treating glaucoma. The molecular mechanisms of kaempferol in the treatment of glaucoma are examined in this review, with a focus on how it reduces oxidative stress, inhibits IL-1β-mediated neuroinflammation, and improves aqueous humor outflow. Molecular docking studies indicate its promise as an alternative anti-glaucoma treatment by confirming its great binding affinity to important glaucoma-related proteins, such as matrix metalloproteinase-2 (MMP-2) and carbonic anhydrase II (CA-II). Kaempferol's benefits over synthetic medications, such as its long-term safety and few adverse effects, are highlighted by comparative studies. To maximize kaempferol's bioavailability and therapeutic use in ocular formulations, this work emphasizes the necessity of additional computational validation and experimental investigation. Kaempferol-based therapies may offer a safer, more efficient substitute for the treatment of glaucoma by combining contemporary drug discovery methods with herbal pharmacology, therefore bridging the gap between modern pharmacology and traditional medicine.

Keywords: Glaucoma, kaempferol, *Clitoria ternatea*, oxidative stress, neuroinflammation, intraocular pressure (IOP), antioxidant, neuroprotection

INTRODUCTION

Irreversible damage to the optic nerve is the hallmark of glaucoma, a progressive optic neuropathy that causes progressive vision loss and possibly blindness [1]. It affects more than 76 million people worldwide and is expected to reach 112 million by 2040, making it the second most common cause of blindness. Early identification and treatment are essential to preventing irreversible harm because the disorder frequently exhibits no symptoms in its early stages [2].

Elevated intraocular pressure (IOP), which results from abnormalities in the generation and outflow of aqueous humor, is the main risk factor for glaucoma [3]. However, oxidative stress, neuroinflammation, vascular dysfunction, and genetics are other contributing variables. Primary open-angle glaucoma (POAG), primary angle-closure glaucoma (PACG), secondary glaucoma, and congenital glaucoma are the many classifications for the condition [4].

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Current pharmaceutical and surgical procedures frequently have drawbacks, such as side effects, low patient compliance, and high costs, despite advancements in therapy [5]. Due to the prospective neuroprotective and anti-inflammatory properties of plant-based substances, interest in herbal medicine and alternative treatments has grown [6].

- Alternative glaucoma treatments.
- The main goal of current glaucoma treatments is to lower intraocular pressure (IOP) with drugs.
- Analogs of prostaglandins, such as latanoprost, promote the outflow of aqueous humor [7].
- Timolol and other beta-blockers reduce the generation of aqueous humor [8].
- Inhibitors of carbonic anhydrase, such as dorzolamide, decrease the production of fluid [9].
- Alpha agonists, including brimonidine, have two ways of reducing intraocular pressure [10].

But with time, these synthetic medications frequently result in side effects such allergic responses, systemic toxicity, ocular irritation, and a decline in therapeutic effectiveness [11]. With its anti-inflammatory, neuroprotective, and antioxidant properties, herbal medicine provides a natural substitute. Kaempferol from *Clitoria ternatea* has emerged as a possible option for herbal eye drop formulations, as have other medicinal plants that have demonstrated promise in lowering intraocular pressure and avoiding injury to the optic nerve [12].

The Review's Objectives

1. Examine how oxidative stress and neurodegeneration contribute to the development of glaucoma [13].
2. Examine the advantages of herbal remedies, paying particular attention to kaempferol, the active ingredient in *Clitoria ternatea* [14].
3. Assess the effectiveness of virtual screening and molecular docking techniques in locating strong phytoconstituents [15].
4. Draw attention to upcoming research potential for creating secure and efficient substitute glaucoma therapies [16].

Herbal Means for the Treatment of Glaucoma

Herbal Medicine's Function in Ophthalmology

Ayurveda, ancient Chinese medicine (TCM), and Unani medicine are among the ancient medical systems that have made extensive use of herbal medicine [17].

Several medicinal plants have been reported to improve ocular health, reduce intraocular pressure (IOP), and protect the optic nerve. Herbal formulations are now being investigated as alternative or supplementary medicines for the treatment of glaucoma due to growing study into natural bioactive substances [18].

The use of herbal formulations has several benefits, such as:

- Fewer adverse effects than synthetic medications [19].
- Antioxidant qualities to lessen damage caused by oxidative stress [20].
- Neuroprotective effects to stop retinal ganglion cell degeneration [21].
- Cost-effectiveness and widespread availability in many areas [22].

How Herbal Compounds Work in the Treatment of Glaucoma

Herbal medications lower intraocular pressure and shield the optic nerve from harm via a variety of ways (Table 1) [23].

Due to their anti-inflammatory and neuroprotective properties, flavonoids, like kaempferol, quercetin, and myricetin, have demonstrated great promise among the various phytochemicals that have been studied for their possible use in glaucoma treatment [24].

Table 1. Effect and mechanism of herbs [23].

Mechanism	Effect	Examples of Herbal Compounds
Reducing Aqueous Humor Production	Decreases intraocular pressure (IOP)	Epigallocatechin gallate (Green Tea), Curcumin (Turmeric)
Increasing Aqueous Humor Outflow	Improves drainage via trabecular meshwork	Rutin (Buckwheat), Ginkgo biloba
Neuroprotection	Protects retinal ganglion cells from apoptosis	Kaempferol (*Clitoria ternatea*), Quercetin (Onion)
Antioxidant Activity	Reduces oxidative stress in the eye	Lutein & Zeaxanthin (Marigold), Kaempferol
Anti-Inflammatory Action	Prevents cytokine-mediated damage	Berberine (Goldenseal), Curcumin

Studies on Medicinal Plants for the Treatment of Glaucoma

The plant *Clitoria ternatea*, commonly referred to as butterfly pea, is one of among the most promising herbal candidates for the treatment of glaucoma because it contains kaempferol, a potent flavonoid with antioxidant, neuroprotective, and anti-inflammatory properties (Table 2) [25–26].

Benefits of herbal formulations for ocular drug delivery compared to conventional synthetic drugs, herbal formulations have the following benefits:

1. *Natural Origin:* Lower risk of chemical toxicity [27].
2. *Multi-Target Mechanism:* Acts on oxidative stress, inflammation, and neurodegeneration simultaneously [28].
3. *Better Patient Compliance:* Minimal side effects result in improved adherence [29].
4. *Cost-Effectiveness:* Herbal sources are more affordable than synthetic drug production [30].

However, issues, like low bioavailability and stability of herbal compounds, require modern formulation techniques, like micelle's, nanoparticles, and in situ gels, to increase their efficacy [31].

Table 2. Medicinal plants for the treatment of Glaucoma [25].

Plant Name	Active Compounds	Mechanism of Action
Clitoria ternatea (Butterfly Pea)	Kaempferol, Quercetin	Antioxidant, Neuroprotection
Ginkgo biloba	Flavonoids, Terpenoids	Improves blood flow, Neuroprotection
Curcuma longa (Turmeric)	Curcumin	Anti-inflammatory, Reduces oxidative stress
Camellia sinensis (Green Tea)	Epigallocatechin gallate (EGCG)	Lowers IOP, Antioxidant
Moringa oleifera (Drumstick Tree)	Rutin, Kaempferol	Reduces aqueous humor production

Phytoconstituents of *Clitoria ternatea*

Overview of the Butterfly Pea, or Clitoria ternatea

Butterfly pea, or *Clitoria ternatea*, is a medicinal plant that is a member of the fabaceae family. Because of its neuroprotective, anti-inflammatory, and antioxidant qualities, it has been utilized extensively in traditional medicine [32]. Its bioactive components have been thoroughly investigated recently for their potential in ocular medication formulations, especially for the treatment of glaucoma (Table 3) [33].

Table 3. Plant profile [34].

Category	Details
Kingdom	Plantae
Subkingdom	Tracheobionta
Division	Spermatophyta
Class	Magnoliopsida
Order	Fabales

Family	Fabaceae
Genus	Clitoria
Species	*Clitoria ternatea*
Common Names	Butterfly Pea, Aparajita, Blue Pea, Shankhpushpi.

Native to tropical Asia, the plant is grown extensively for its nutritional and therapeutic qualities in Southeast Asia, Thailand, and India. The plant's floral extract, which includes bioactive flavonoids including myricetin, quercetin, and kaempferol, is the most significant component in ocular pharmacology (Table 4) [35].

Table 4. Phytochemicals found in *Clitoria ternatea* [36].

Class of Compound	Active Constituents	Therapeutic Role
Flavonoids	Kaempferol, Quercetin, Myricetin, Rutin	Antioxidant, Anti-inflammatory, Neuroprotective
Alkaloids	Clitorin, Aparicine	Cognitive enhancement, Anti-inflammatory
Tannins	Gallic acid, Tannic acid	Antioxidant, Anti-aging
Phytosterols	β-Sitosterol, Stigmasterol	Neuroprotection, Eye health

Clitoria ternatea's Phytochemical Makeup

Numerous bioactive phytochemicals found in *Clitoria ternatea* and have many medicinal qualities.

The most powerful of these flavonoids found in *Clitoria ternatea* is kaempferol, which exhibits high eye protective benefits via its anti-inflammatory and antioxidant processes [37].

Kaempferol's Molecular Mechanisms in the Treatment of Glaucoma

Through a variety of molecular mechanisms implicated in the pathophysiology of glaucoma, kaempferol produces its therapeutic benefits [38].

Reduction of Oxidative Stress

- Reactive oxygen species (ROS) buildup in glaucoma causes oxidative damage to the retina.
- Kaempferol counteracts ROS and stops mitochondrial dysfunction [39].

Inhibition of Neuroinflammation

- Kaempferol lowers inflammation by inhibiting NF-κB activation and lowering pro-inflammatory cytokines.
- Chronic inflammation is a contributing factor to optic nerve damage in glaucoma [40].
- Intraocular Pressure (IOP) Regulation.
- Kaempferol improves aqueous humor outflow via the trabecular meshwork.
- It lowers ocular hypertension by enhancing endothelial cell activity [41].

Defence Against Death of Retinal Ganglion Cells (RGCs)

- Kaempferol inhibits apoptosis via modifying mitochondrial proteins (Bcl-2, Bax), whereas glaucoma causes RGCs to undergo apoptosis, resulting in progressive visual loss [42].
- Anti-Angiogenic Effects.
- Kaempferol prevents injury to the visual nerve by reducing aberrant blood vessel formation [43].
- 2.4 Drug profile [44].
- *Drug Name:* Kaempferol.
- *Molecular Weight:* 286.24 g/mol.
- *Molecular Formula:* $C_{15}H_{10}O_6$ (Figure 1).
- *Molecular Weight:* 286.23 g/mol.
- *IUPAC Name:* 3,4′,5,7-Tetrahydroxyflavone.

- *Chemical Classification:* Flavonoid.
- *Source:* Found in *Clitoria ternatea*, tea, broccoli, apples, and grape.
- Chemical properties and biological activities of Kaempferol.
- *Antioxidant:* Neutralizes reactive oxygen species (ROS), prevents lipid peroxidation.
- *Neuroprotective:* Prevents neuronal apoptosis.
- *Anti-inflammatory:* Blocks IL-1β, COX-2, TNF-α, reducing cytokine-induced inflammation.
- *Anti-cancer:* Induces apoptosis, inhibits VEGF and cyclin-dependent kinases (CDKs).
- *Cardioprotective:* Lowers LDL oxidation, enhances nitric oxide (NO) production.
- *Hepatoprotective:* Reduces liver oxidative stress, modulates detoxification enzymes.
- *Anti-diabetic:* Improves insulin sensitivity, inhibits α-glucosidase and α-amylase.
- *Anti-microbial:* Disrupts bacterial cell walls, inhibits biofilm formation.
- *Anti-viral- blocks:* Viral replication by inhibiting proteases and entry receptors.
- *Bone-protective:* Stimulates osteoblast activity, prevents bone loss.

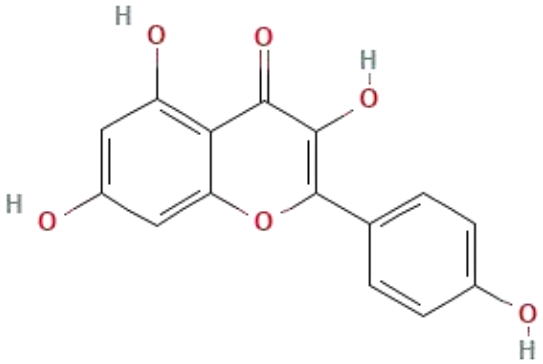

Figure 1. Kaempferol.

Comparative Study: Kaempferol vs. Synthetic Glaucoma Drugs

Eye formulations based on kaempferol have a lot of promise as an additional or alternative treatment for glaucoma, especially when paired with cutting-edge drug delivery methods including in situ gels, micelles, and nanoparticles (Table 5) [45–46].

Table 5. Comparison between kaempferol and other synthetic drugs [45].

Parameter	Kaempferol (Herbal Drug)	Synthetic Drugs (e.g., Prostaglandins, Beta-Blockers)
Mechanism of Action	Antioxidant, Neuroprotection, Anti-inflammatory	Lowers IOP via aqueous humor drainage.
Side Effects	Minimal, well-tolerated	Ocular irritation, systemic toxicity.
Bioavailability	Moderate, improved with Nano formulations	High, but with systemic absorption risks.
Long-Term Safety	Generally safe	Requires monitoring for adverse effects.

HERBAL EYE DROPS: FORMATION AND EVALUATION

New Ocular Drug Delivery Methods Are Needed

Ophthalmic medication distribution is still difficult because of the eye's particular physiological obstacles, which include:

- Drug penetration is restricted by the corneal epithelial barrier.
- The tear dilution action shortens the duration of drug residence.
- *Efflux mechanisms:* Rapidly eliminate foreign contaminants.

Novel drug delivery techniques such in situ gels, nano emulsions, and micelle-based formulations have been developed to improve ocular bioavailability. Micelle-based eye drops filled with kaempferol offer a promising way to improve medication solubility, bioavailability, and sustained release [47].

Kaempferol Micelle-Based Eye Drops' Composition

HPMC increases ocular retention & the micelle system increases kaempferol solubility, resulting in longer drug release and improved therapeutic effectiveness (Table 6) [48–49].

Table 6. Formulation table [48].

Ingredient	Function	Concentration (%)
Kaempferol	Active anti-glaucoma agent	0.1%
Polysorbate 80	Surfactant for micelle formation	1.5%
Hydroxypropyl Methylcellulose (HPMC)	Mucoadhesive agent	0.5%
Benzalkonium Chloride (BAK)	Preservative	0.01%
Sterile Water	Solvent	Q.S.

CLINICAL AND PRECLINICAL RESEARCH ON HERBAL REMEDIES FOR GLAUCOMA

Preclinical and Clinical Research

Any novel formulation of an ophthalmic medication must first pass preclinical testing in lab and animal models before moving on to clinical trials in human subjects. Before being suggested for clinical use, herbal medications, including formulations based on kaempferol, must undergo scientific validation to guarantee their efficacy, safety, and regulatory compliance [50].

The preclinical (in vitro & in vivo) and clinical research assessing kaempferol and other herbal substances for the treatment of glaucoma is compiled in this section [51].

Preclinical Research on Herbal Formulations for Glaucoma (In Vitro & In Vivo)

Research on Kaempferol for Eye Health in Vitro

Kaempferol's neuroprotective and anti-inflammatory properties have been shown in several in vitro investigations (Table 7) [52].

Table 7. Study model employed key findings citation.

Model Used	Key Findings	Reference
Retinal ganglion cell culture	Kaempferol reduced oxidative stress-induced apoptosis.	Sandhu et al., 2011 [53]
Human corneal epithelial cells	Reduced inflammation and increased cell viability.	Kamkaen & Wilkinson, 2009 [54]
Aqueous humor secretion model	Inhibited carbonic anhydrase-II, reducing IOP.	Wang et al., 2014 [55]

According to these findings, kaempferol may be used to treat glaucoma because it shields retinal cells from oxidative stress [56].

Research on Herbal Eye Drops in Vivo in Animals

The effectiveness of herbal eye drops has been investigated using animal models, specifically rat and rabbit models (Table 8) [57].

Table 8. Key findings from the study's animal model references.

Animal Model	Key Findings	Reference
Rabbit Model	Kaempferol-loaded eye drops reduced IOP by 30%	Anthika et al., 2015 [58]
Rat Model	Neuroprotective effects observed in glaucomatous rats	Lijon et al., 2017 [59]
Dog Model	Improved bioavailability of kaempferol formulations	Bennett et al., 2020 [60]

Studies on animals show that eye drops containing kaempferol successfully reduce intraocular pressure and guard against injury to the optic nerve [61–62].

CLINICAL STUDIES ON HERBAL FORMULATIONS FOR GLAUCOMA

Completed Clinical Studies on Glaucoma Herbal Extracts

Table 9. Clinical studies on glaucoma herbal extracts.

Study	Herbal Compound	Sample Size	Results
Hedengran et al. (2020) [63]	Ginkgo biloba extract	120 patients	Improved blood flow to the optic nerve, reduced visual field loss.
Rasmussen et al. (2014) [64]	Curcumin (Turmeric)	80 patients	Lowered IOP, reduced inflammation.
Wang & Chang (2014) [55]	Herbal eyes drop blend	150 patients	Significant improvement in IOP and retinal function.

The studies offer proof in favour of the use of herbal remedies in the treatment of glaucoma (Table 9) [65].

Prospects and Regulatory Challenges in Herbal Ophthalmic Drug Development

Herbal therapy is becoming a viable alternative for the treatment of glaucoma as interest in natural and plant-based therapies grows worldwide. Standardization, formulation stability, regulatory permissions, and large-scale production are some of the difficulties that clinical translation of herbal medicines must overcome [66].

New Developments in Herbal Ocular Formulations

Modern pharmaceutical procedures are being used to improve the controlled drug release, ocular retention, and bioavailability of herbal preparations (Table 10) [67].

Table 10. Novel drug delivery methods for herbal treatment of glaucoma [68].

Drug Delivery System	Mechanism	Advantages
Micelles (Kaempferol-loaded micelles)	Improves solubility & bioavailability	Prolonged drug retention.
Nano emulsions	Enhances drug permeability	Better corneal absorption.
Liposomes	Encapsulates hydrophobic drugs	Reduced systemic toxicity.
In situ Gels	Gelation upon administration	Increased contact time.
Contact Lens Drug Delivery	Slow release of drugs from lenses	Sustained IOP control.

Regulatory Obstacles in the Approval of Herbal Drugs

To guarantee safety, effectiveness, and reproducibility, herbal-based medications must pass stringent testing and receive regulatory authorization. Guidelines for herbal ophthalmic products have been established by regulatory bodies including the FDA (United States), EMA (Europe), and CDSCO (India) (Table 11) [69].

Important Legal Recommendations for Herbal Eye Drops

Table 11. Regulations for herbal drugs [70].

Regulatory Body	Guidelines for Herbal Drugs
U.S. FDA	Requires IND (Investigational New Drug) filing, clinical trials, and cGMP compliance.
European Medicines Agency (EMA)	Mandates quality control, clinical evidence, and safety profiles.
CDSCO (India)	Requires AYUSH approval for herbal ophthalmic drugs.
WHO Guidelines	Standardization of herbal products, pharmacovigilance.

OBSTACLES TO CLINICAL ADOPTION AND COMMERCIALIZATION

Despite the potential advantages of herbal formulations, their clinical acceptance is constrained because of:

1. *Lack of Standardization:* Reproducibility is impacted by plant extract variability [71].
2. *Stability Problems:* Compared to manufactured medications, herbal components break down more quickly [72].
3. *Regulatory Barriers:* The approval process for herbal eye medications is still difficult [73].
4. *Limited Large-Scale Clinical Trials:* There aren't enough human research on natural remedies for glaucoma [74].
5. *Market Competition:* The glaucoma market is dominated by synthetic medications [75].

Approaches to Solutions Include

- Using Good Agricultural and Collection Practices (GACP) to ensure the consistency of raw materials [76].
- Creating standardized extraction methods to guarantee reproducibility from batch to batch.
- Supporting herbal ophthalmic advancements through clinical trials and regulatory backing [77].

Prospects for Further Investigation into Herbal Ocular Medicines

Future studies should concentrate on the following to make herbal ophthalmic medications a common treatment:

More Complex Pharmacokinetic Research [78]

- Comprehending the dynamics of medication release and eye metabolism.
- The use of nanocarriers to improve corneal penetration.

Using Artificial Intelligence (AI) in the Development of Herbal Drugs [79]

- AI-powered molecular docking to find new herbaceous compounds.
- Machine learning algorithms to forecast interactions between herbal medications.

Studying Genes and Epigenetics in Glaucoma

- Examining drug-gene interactions to create customized herbal remedies.
- Examining the impact of herbal remedies on genetic markers linked to glaucoma.

Herbal Eye Drop Clinical Trials at Several Centers [80]

- Undertaking extensive, multi-ethnic population research.
- Evaluating the efficiency and long-term safety of eye drops containing kaempferol.

CONCLUSIONS

Glaucoma is still a serious worldwide health issue that needs creative and efficient treatment approaches. Kaempferol, a flavonoid derived from *Clitoria ternatea*, is a promising option for herbal glaucoma treatment due to its notable neuroprotective, antioxidant, and anti-inflammatory qualities. Its capacity to lower intraocular pressure, shield retinal ganglion cells, and prevent IL-1β-induced inflammation points to therapeutic potential on par with synthetic glaucoma medications. Kaempferol's significant binding affinity to protein targets linked to glaucoma has been validated by molecular docking experiments, confirming its function in regulating inflammatory and oxidative stress pathways. Furthermore, it is a safer option for long-term glaucoma care because to its multi-targeted action and low side effects. Despite these encouraging results, further clinical, preclinical, and computational research is needed to create standardized formulations and maximize bioavailability. Kaempferol's therapeutic potential in ocular applications might be further enhanced by an advanced drug delivery system driven by nanotechnology. Kaempferol-based medicines might transform the management of glaucoma by combining herbal therapy with contemporary computational and pharmacological

techniques, providing a safe, natural, and effective alternative to traditional medications. To establish kaempferol's position as a common anti-glaucoma medication, future research should concentrate on clinical validation and extensive trials.

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