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A Comprehensive Review on The Ocular Delivery Potential Of Clitoria Ternatea Anthocyanins Using Novel Drug Delivery Systems

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Abstract

Anthocyanins are naturally occurring pigments that easily dissolve in water and are well-known for their strong antioxidant and anti-inflammatory properties. These characteristics make them interesting for eye-related treatments, where oxidative stress and irritation often worsen existing conditions. Unfortunately, most eye drops do not stay on the eye long enough, which leads to extremely low drug absorption. Because of this, researchers are trying to develop dosage forms like thin films, hydrogels, inserts and nanoparticles that remain on the eye surface for longer periods.

Clitoria ternatea (commonly called butterfly pea) is one of the most abundant natural sources of stable anthocyanins, especially a group known as ternatins. These compounds show unique color changes with variations in pH, have good solubility in water and possess strong free-radical-scavenging activity. This review highlights the plant's chemistry, traditional uses, extraction methods for anthocyanins and the growing interest in using these compounds in modern ocular drug delivery. The review also points out existing limitations and areas where more research is needed.

Keywords

Anthocyanins, Clitoria ternatea, Ocular delivery, NDDS, Ocular films, Antioxidant activity

1. Introduction

Clitoria ternatea is a climbing plant widely found in India and other tropical countries. Its blue flowers are commonly used in traditional preparations and have attracted scientific attention because they contain large quantities of anthocyanins. These pigments belong to the flavonoid group and, along with other chemical constituents of the plant, contribute to its medicinal value.

Delivering drugs to the eye is always difficult. The eye naturally removes foreign materials through tear secretion, blinking and drainage into the nasal cavity. Because of these mechanisms, most of the drug applied as eye drops is washed away in a very short time, and only a tiny part reaches internal tissues. This challenge has encouraged researchers to explore different delivery systems that stay on the ocular surface for longer and gradually release the drug.

The anthocyanins present in *Clitoria ternatea*, mainly the ternatin group, show strong antioxidant effects and can help protect sensitive eye tissues from oxidative and inflammatory damage. Their water solubility and stability under acidic conditions also make them suitable for incorporation into modern ocular formulations

such as hydrogels, nanoparticles and thin films. Considering these medicinal and chemical characteristics, understanding the pharmacognostic and phytochemical profile of *Clitoria ternatea* becomes essential.

2. Pharmacognosy

Biological Source

The drug consists of the dried seeds and aerial parts of *Clitoria ternatea*, a perennial climber from the Fabaceae family.

Synonyms

C. albiflora, C. bracteata, C. mearnsii, C. tanganicensis, C. zanzibarensis

Family: Fabaceae
Genus: Clitoria

Species:*C.ternatea*

Traditional Uses

In many traditional systems, different parts of the plant are used for improving memory and concentration, soothing throat irritation, reducing swelling and managing certain skin complaints. Both the roots and leaves appear in various formulations, while the flower extract is also traditionally used for its calming and detoxifying properties. Herbal tea made from the flowers is also used for weight management.

Plant Parts Used

Flowers, leaves, seeds, bark, stems, sprouts and fruits.

fig 1: herbal tea

3. Chemical Constituents

The plant contains multiple groups of phytochemicals:

Triterpenoids

Taraxerol, Taraxerone

Flavonoids and Glycosides

Kaempferolderivatives

Flavonol-3-glycosides

Anthocyanins (Major)

TernatinsA1–A3
TernatinsB1–B4
TernatinsC1–C5
TernatinsD1–D3

Other Constituents

Phenolic acids, phytosterols, sugars, long-chain alcohols and an antimicrobial protein known as finotin.

4. Pharmacological Activities

fig 2: pharmacological activity

4.1. Antioxidant Activity

Clitoria ternatea contains high levels of anthocyanins, particularly ternatins, which exhibit potent free-radical scavenging activity capable of neutralizing ROS like superoxide and hydroxyl radicals. These pigments stabilize reactive molecules through electron donation, preventing oxidative damage to lipids and proteins in ocular tissues. The extract also enhances endogenous antioxidant enzymes such as catalase and superoxide dismutase, further strengthening cellular defense. Studies have shown that Clitoria extracts effectively reduce lipid peroxidation in corneal epithelial cells and protect the eye from UV-induced oxidative changes (Mukherjee et al., 2008). This antioxidant capacity makes it a promising natural agent for delaying or preventing ocular diseases associated with oxidative stress.

4.2. Anti-inflammatory Activity

The anthocyanin-rich extract demonstrates strong anti-inflammatory effects by inhibiting key enzymes such as COX-2 and LOX, reducing prostaglandin and leukotriene synthesis responsible for inflammation. It also suppresses inflammatory cytokines including TNF-α, IL-1β, and IL-6, which are major contributors to ocular irritation and swelling. Animal models show significant reduction in induced edema and inflammatory intensity following administration of Clitoria extracts these anti-inflammatory actions support their potential use in managing conjunctivitis, allergic responses, and surface irritation of the eye.

4.3. Neuroprotective Activity

Clitoria ternatea is widely reported for its nootropic properties, showing enhanced learning and memory in rodent models. It improves acetylcholine levels by upregulating choline acetyltransferase, leading to improved neuronal signaling. The extract protects neuronal cells from ROS-induced apoptosis by limiting oxidative stress within nerve tissues. These effects are highly relevant to ocular neuroprotection, especially in diseases such as glaucoma, where retinal ganglion cells undergo oxidative degeneration. The neuroprotective profile therefore links Clitoria to potential vision-preserving effects.

4.4. Anti-diabetic Activity

Butterfly pea extracts support glucose regulation by enhancing insulin sensitivity and promoting peripheral glucose uptake. They also inhibit digestive enzymes such as α-amylase and α-glucosidase, helping reduce postprandial glucose spikes. In diabetic models, extracts improved fasting glucose levels, lipid profiles, and oxidative balance. Since diabetes accelerates oxidative stress that damages retinal and corneal cells, Clitoria's antidiabetic activity indirectly protects ocular tissues from diabetic complications.

4.5. Antimicrobial Activity

Clitoria ternatea exhibits broad-spectrum antimicrobial action due to its phenolics, flavonoids, and antimicrobial protein "finotin". The extract is active against common ocular pathogens such as *Staphylococcus aureus, E. coli, Pseudomonas aeruginosa,* and *Candida albicans*. It disrupts microbial membranes and interferes with enzyme activity, ultimately leading to cell death. This activity is particularly useful in formulating antimicrobial eye drops or ocular films, especially preservative-free systems where contamination risk is high.

4.6. Wound Healing Activity

Extracts of Clitoria ternatea promote wound healing by stimulating collagen synthesis, enhancing fibroblast migration, and accelerating epithelial regeneration. The antioxidant and anti-inflammatory actions reduce oxidative load and tissue swelling, supporting faster recovery. In addition, the extract enhances angiogenesis, improving nutrient delivery to injured areas. These mechanisms make Clitoria suitable for corneal wound healing, particularly after abrasions or surface injuries.

4.7. Anti-carcinogenic Activity

Clitoria ternatea shows promising anti-cancer potential, with studies demonstrating its ability to induce apoptosis by activating caspase pathways. Anthocyanins suppress abnormal cell proliferation by downregulating pathways like NF-κB and MAPK. The extract also inhibits angiogenesis, which is essential for tumor growth. Its antioxidant molecules protect DNA from oxidative mutations, reducing carcinogenic risk. Although not yet explored in ocular oncology, these mechanisms may contribute to preventing oxidative DNA damage in eye tissues.

5. Extraction Methods for Anthocyanins

Ultrasound-Assisted Extraction (UAE)

According to the ultrasonic extraction approach reported by Bea Anthika et al., *Clitoria ternatea* flowers were used as the source of water-soluble anthocyanins for ophthalmic applications.

Fresh butterfly pea flowers were first washed thoroughly to remove surface impurities and then subjected to size reduction. The plant material was mixed with distilled water as the extraction solvent, avoiding the use of organic solvents to ensure safety for ocular use.

The mixture was placed in an ultrasonic bath, where extraction was carried out using ultrasonic waves to enhance pigment release. Sonication promotes cavitation phenomena, which disrupts the plant cell matrix and improves mass transfer of anthocyanins into the aqueous medium. The extraction was performed under controlled temperature conditions to prevent degradation of heat-sensitive anthocyanins.

After sonication, the extract was separated from plant residues by filtration. To obtain a sterile extract suitable for eye drop formulation, the filtrate was further subjected to ultrafiltration using membrane filtration techniques. This step effectively removed microbial contaminants and particulate matter without affecting the chemical integrity of anthocyanins. The resulting extract was a clear, sterile, anthocyanin-rich solution suitable for ophthalmic formulation studies.

This ultrasound-assisted aqueous extraction method offers advantages such as reduced extraction time, elimination of organic solvents, enhanced extraction efficiency and direct applicability for ophthalmic drug delivery systems.

6. Ocular Drug Delivery Challenges

Major obstacles for ocular delivery include:

- Continuous tear production
- Blinking
- Nasolacrimal drainage
- Tight corneal epithelium
- Rapid loss of eye drops

Due to these natural defenses, topical medications often have very low bioavailability.

7. Novel Ocular Drug Delivery Systems (NDDS)

7.1. Ocular Films

Ocular films are thin, transparent polymeric strips designed to adhere to the ocular surface and provide extended contact time, improving drug retention significantly compared to conventional drops. These films can be prepared using polymers such as HPMC, PVA, chitosan, or alginate, which allow flexible drug loading and sustained release. Their small size and flexibility make them comfortable for patients, while the absence of preservatives enhances safety.

Drug release occurs through diffusion or polymer erosion, ensuring prolonged therapeutic availability over several hours. Such films are stable, easy to sterilize and offer accurate dosing, making them suitable for water-soluble compounds like anthocyanins. Research has shown that ocular films can increase bioavailability 3–5 times higher than eye drops. Due to their controlled release properties, ocular films are considered ideal for chronic eye conditions requiring long-term therapy.

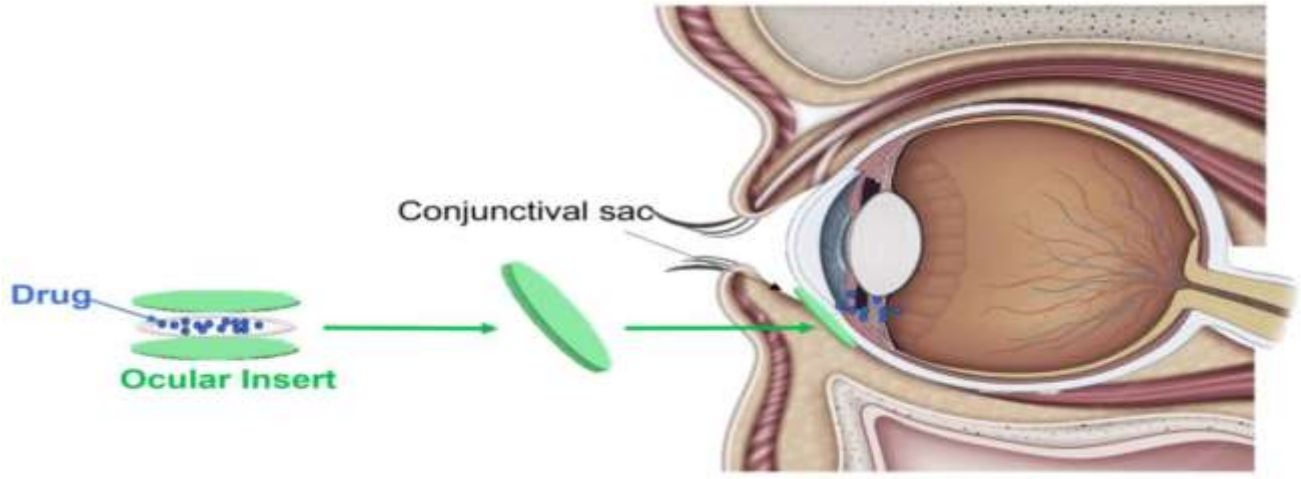

fig.3: ocular films

7.2. Ocular Inserts

Ocular inserts are solid or semi-solid drug delivery devices placed in the conjunctival sac, offering prolonged and controlled release through diffusion, osmosis, or erosion. They may be soluble, bioerodible, or non-biodegradable depending on the polymer used. Inserts such as Ocusert and Lacrisert are well-known examples demonstrating their clinical usefulness. Because inserts maintain intimate contact with the eye, drug loss due to tears and blinking is minimized, improving bioavailability significantly.

They also maintain a constant drug level, avoiding the peaks and dips associated with drops. Inserts reduce dosing frequency and enhance patient compliance, making them suitable for long-term treatments. For hydrophilic compounds like anthocyanins, bioerodible inserts help protect the active molecules from degradation and promote sustained therapeutic action.

7.3. In-situ Gelling Systems

In-situ gels are liquid formulations that transform into gels when exposed to physiological conditions such as pH, ions or temperature. This phase transition allows the formulation to spread easily when instilled and then convert to a gel that resists drainage. Polymers like alginate, gellan gum, carbopol and poloxamers are commonly used because they form clear, stable gels. Once gelled, they provide prolonged residence time and controlled drug release for several hours. These systems are comfortable to administer due to their initial liquid nature, but offer the advantages of gels such as increased viscosity and bioadhesion. For anthocyanins, in-situ gels are particularly beneficial as they help protect the sensitive pigments from degradation and allow gradual release. Studies show significantly improved ocular drug bioavailability with ion-activated gelling systems.

7.4. Hydrogels

Hydrogels are soft, water-rich polymer networks capable of holding large amounts of fluid, making them similar to natural ocular tissues. Their high water content ensures excellent biocompatibility, transparency and comfort. Drugs are incorporated within the hydrogel matrix and are released gradually through diffusion. Hydrogels made from PVA, hyaluronic acid, polyacrylic acid or chitosan have shown promise in ocular applications. Because hydrogels maintain hydration, they help stabilize sensitive molecules like anthocyanins, preventing rapid degradation.

Their bioadhesive properties also increase residence time on the eye surface. Hydrogels can be formulated as preformed gels or in-situ forming systems depending on clinical need. They provide sustained release, ease of application and minimal irritation, making them suitable carriers for antioxidant-based ophthalmic therapy.

7.5. Contact Lens–Based Delivery

Contact lens–based systems incorporate drug molecules directly into the lens matrix, allowing continuous delivery over extended wear time. Drug loading may be achieved through soaking, molecular imprinting or nano-carrier embedding, which helps achieve sustained release for several hours to days. Because the lens remains in close contact with the cornea, drug absorption improves dramatically often 20–50 times higher than that of eye drops.

This system minimizes drug wastage, avoids frequent dosing and enhances patient comfort. Incorporating antioxidants like anthocyanins into hydrophilic lenses helps protect them from environmental degradation and ensures stable release. Contact lenses also bypass issues like rapid tear washout. Recent studies demonstrate that modified lenses with vitamin-E coatings or nanoparticle reservoirs can further extend drug release duration.

Why *Clitoria ternatea Anthocyanins* Are Suitable for Ocular Use

- Strong antioxidant protection
- Anti-inflammatory effects
- High water solubility
- Naturally safe and biocompatible
- pH-responsive nature suitable for smart systems
- Ternatins remain stable under acidic conditions

Limitations of Current Research

- Very few in-vivo studies
- Instability at neutral/alkaline pH
- Low corneal permeation
- Need for advanced nanocarriers
- Lack of clinical evidence
- No standardized dosage guidelines

Future Scope

- Nanoparticle-based anthocyanin delivery
- Human clinical trials
- Development of pH-triggered eye drops
- Hydrogel-based ocular inserts
- Combination therapy with other antioxidants
- Preservative-free formulations

Future research may explore the integration of ultrasound-extracted and ultrafiltered anthocyanins into advanced ocular delivery platforms such as nanoparticles and pH-triggered in-situ gels to further enhance bioavailability and therapeutic efficacy.

8. Methodology

This review is based on published articles from scientific databases such as PubMed, ScienceDirect, Scopus, Google Scholar and thesis repositories. Literature from 2000–2025 focusing on extraction, formulation and pharmacological aspects of *Clitoria ternatea* was included.

9. Conclusion

The anthocyanins present in *Clitoria ternatea* show strong antioxidant, anti-inflammatory and protective effects, making them promising for ocular applications. Although conventional eye drops have very poor

retention and absorption, new systems like nanoparticles, hydrogels, in-situ gels and thin films show potential to overcome these challenges. Future research should aim at improving stability, enhancing penetration and conducting clinical trials to fully establish their role in ophthalmic therapy.

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