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OCULAR ANTIMICROBIAL POTENTIAL OF PITHECELLOBIUM DULCE LEAVES: A PHYTOPHARMACOLOGICAL INSIGHT

Mohammedkabeer A.[1]*, Dr. C. Jothimanivannan[2], Sathya Jasmine A.[1], Kiruthika P.[1], JothiPrakash P[1], Sundhar S.[1]

[1]Student, SS Institute of Pharmacy, Sankari, Salem - 637301.

[2]Professor & Principal, SS Institute of Pharmacy, Sankari, Salem - 637301.

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***Corresponding Author**
Mohammedkabeer A.
Student, SS Institute of Pharmacy, Sankari, Salem - 637301.

ABSTRACT

The increasing incidence of ocular infections and the emergence of antimicrobial resistance have prompted a renewed interest in plant-based therapeutics for eye care. Pithecellobium dulce, commonly known as Manila tamarind, is a tropical plant traditionally used in folk medicine for various ailments. Recent phytochemical and pharmacological investigations have revealed the therapeutic promise of its leaves, particularly in antimicrobial applications. This review explores the potential of P. dulce leaf extracts in managing ocular infections, emphasizing their bioactive constituents, mechanisms of antimicrobial action, and compatibility with ocular tissues. The leaves of *P.* dulce are rich in flavonoids, tannins, alkaloids, phenolic compounds, and glycosides—all known for their antimicrobial, anti-inflammatory, and antioxidant activities. These compounds exert bactericidal and bacteriostatic effects by disrupting microbial cell walls, inhibiting protein synthesis, and generating reactive oxygen species. The review also compiles evidence from in vitro studies where P. dulce leaf extracts exhibited significant antimicrobial activity against ocular pathogens such as Staphylococcus aureus, Pseudomonas aeruginosa, and Escherichia coli. In addition to its antimicrobial effects, the anti-inflammatory properties of the leaf extract may help reduce ocular inflammation associated with infections like conjunctivitis and blepharitis. The safety and biocompatibility of herbal extracts in ophthalmic formulations are also addressed, considering the delicate nature of the ocular surface. Moreover, the integration of P. dulce in novel drug delivery systems such as ocular gels, eye drops, and nanoparticle-based carriers is discussed, presenting opportunities for enhanced bioavailability and

sustained release. This review emphasizes the need for clinical trials and formulation optimization to translate the pharmacological benefits of P. dulce into mainstream ophthalmic therapies. In conclusion, Pithecellobium dulce leaf extract represents a promising, underexplored phytopharmaceutical candidate for developing herbal treatments against ocular infections. Its rich phytochemistry, proven antimicrobial properties, and potential for safe ocular use make it a valuable alternative in the fight against antibiotic-resistant eye pathogens.

KEYWORDS: *Pithecellobium dulce, Ocular infections, Antimicrobial activity, Phytopharmacology, Herbal eye drops, Conjunctivitis, Traditional medicine.*

INTRODUCTION

Ocular infections represent a significant public health concern worldwide, affecting millions annually and ranging in severity from mild conjunctivitis to vision-threatening keratitis and endophthalmitis. The most common causative agents include bacteria such as Staphylococcus aureus, Pseudomonas aeruginosa, and Escherichia coli, as well as certain fungi and viruses. These infections can cause discomfort, visual impairment, and even permanent blindness if not treated appropriately. While conventional antimicrobial therapies—particularly antibiotic and antifungal eye drops—remain the mainstay of treatment, growing antimicrobial resistance and drug-associated side effects have fueled a demand for safer, more effective, and sustainable alternatives.

In recent years, medicinal plants have gained renewed attention for their potential role in combating microbial resistance and providing natural alternatives for ocular therapeutics. Plant-based compounds, particularly those derived from ethnomedicinal sources, offer a wide array of bioactive phytochemicals with proven antimicrobial, anti-inflammatory, and antioxidant properties. Among these, Pithecellobium dulce (Roxb.) Benth., commonly known as Manila tamarind, emerges as a promising candidate due to its rich ethnopharmacological history and potent phytochemical profile.

P. dulce is a fast-growing, drought-tolerant leguminous tree native to Central America and widely cultivated in tropical and subtropical regions, including India and Southeast Asia. Various parts of the plant—especially the leaves, bark, and fruits—have been traditionally used to treat a wide spectrum of ailments such as gastrointestinal disturbances, respiratory infections, skin diseases, and ocular complaints. Leaf extracts, in particular, are applied in

traditional systems of medicine to alleviate eye redness, itching, and discharge, suggestive of conjunctivitis or microbial infection.

Phytochemical investigations have shown that P. dulce leaves are rich in flavonoids, tannins, alkaloids, and phenolic compounds—classes of molecules known for their antimicrobial and antioxidant effects. These constituents are believed to act through multiple mechanisms, including inhibition of microbial enzyme systems, disruption of cell membranes, and modulation of host inflammatory responses, making them suitable for managing complex ocular infections.

Despite its traditional use and promising phytochemical content, the ocular application of P. dulce remains underexplored in modern scientific literature. There is limited consolidated evidence examining its phytopharmacological relevance to ophthalmology, particularly in the context of formulating herbal eye drops, ocular gels, or nanocarriers.

This review aims to fill that gap by providing a comprehensive analysis of the botanical, ethnomedicinal, phytochemical, antimicrobial, and ocular pharmacological aspects of Pithecellobium dulce leaves. It further evaluates their therapeutic potential against ocular pathogens and discusses prospects for developing novel plant-based ophthalmic formulations. The goal is to bridge the gap between traditional knowledge and modern ocular pharmacotherapy, promoting the integration of safe, effective, and sustainable natural agents into mainstream eye care.[1]

Biological source

Botanical Name: Pithecellobium dulce

Family Name: Leguminosae

Parts Used: Bark, leaves, seeds, flowers, pulp

Common names

Hindi: Vilayati imli, Jungli jilebi

Marathi: Ingraji chinch

Tamil: KodukkaPuli

English: Manila Tamarind, Monkey pod, Madras[2]

Methods of collection

1. Collection of Plant Leaves

- Leaves of Pithecellobium dulce were collected from the local areas of Rohtak district, Haryana, in July 2010.

2. Cleaning of Plant Material

- The collected leaves were thoroughly washed first with tap water and then with distilled water to remove any dust or debris.

3. Drying Process

- The clean leaves were dried in an oven at 40°C.

4. Preparation and Storage

- The dried leaves were ground into a fine powder and stored in airtight containers at room temperature until further use.[3]

Chemical Constituents

- The plant contains about 25% tannins and 18% fixed oil (like olein).
- A natural compound called quercetin (a flavonoid) has been found
- The seeds have various useful substances such as steroids, saponins, fats, phospholipids, glycosides, glycolipids, and sugars (polysaccharides)
- The bark contains a high amount of tannins (about 37%), mainly of the catechol type.
- The leaves contain quercetin, kaempferol, dulcitol, and afezilin.
- Seed oil has 9 types of saturated and 17 types of unsaturated fatty acids.
- Protein content is highest in seeds (about 50–67%), then in stems, roots, leaves, flowers, and fruits.
- An alcohol extract (ethanol) of fruits gave ten different compounds, such as:
- 2,5,6-trimethyl-1,3-oxathiane
- trans-3-methyl-2-N-propylthiophane
- 2-furancarboxaldehyde-5-(hydroxymethyl)
- D-pinitol
- Heptacosanoic acid
- Hexadecanoic acid[4]

Botanical and Ethnopharmacological Background of *Pithecellobium dulce*

Botanical Description

Pithecellobium dulce (Roxb.) Benth., commonly known as Manila tamarind, is a fast-growing, perennial leguminous tree belonging to the family Fabaceae (subfamily Mimosoideae). It is native to Central America and northern South America but has been widely introduced in tropical and subtropical regions, including India, the Philippines, Southeast Asia, and parts of Africa.

The tree typically grows up to 15–20 meters in height, characterized by a broad crown and thorny branches. Its leaves are bipinnately compound, comprising one pair of pinnae and two pairs of leaflets, which are obovate to elliptical in shape and dark green in color. The plant bears small, greenish-white, fragrant flowers clustered in terminal panicles. Its fruits are leguminous pods that are spiral-shaped, fleshy, and pinkish-red when ripe. These pods contain edible, pulpy arils surrounding hard, black seeds.[5]

Geographical Distribution and Habitat

P. dulce is a highly adaptable species that thrives in various environmental conditions, including arid, semi-arid, and humid climates. It is frequently found along roadsides, in wastelands, and in agroforestry systems. The plant is drought-tolerant and can grow in a range of soil types, including alkaline, saline, and nutrient-poor soils, which makes it a valuable species for afforestation and land reclamation projects.

In India, P. dulce is extensively found in the southern and western states such as Tamil Nadu, Karnataka, Andhra Pradesh, and Maharashtra. Its rapid growth, nitrogen-fixing ability, and minimal maintenance requirements have made it a preferred choice for shade and erosion control in tropical agricultural regions.[6]

Traditional and Ethnopharmacological Uses

Historically, various parts of P. dulce have been used in indigenous medicine systems, including Ayurveda, Siddha, and folk medicine traditions in Latin America and South Asia. The plant is revered for its multipurpose utility, serving nutritional, therapeutic, and ecological functions.

Leaves

The leaves of P. dulce are perhaps the most pharmacologically active part of the plant. In traditional medicine, crushed leaves are used topically to treat skin infections, boils, and ulcers due to their antiseptic and anti-inflammatory properties. Decoctions made from leaves have also been used orally for treating fever, gastrointestinal disorders, and respiratory issues like bronchitis and sore throat.

Importantly, eye infections such as conjunctivitis and irritation have been treated traditionally using leaf infusions or juice applied topically. The anti-inflammatory and antimicrobial properties of the leaves make them suitable for such applications, although scientific validation is only beginning to emerge.

Bark and Roots

The bark of P. dulce is astringent and has been traditionally used to treat dysentery, diarrhea, and hemorrhoids. In some regions, it is used in gargles for throat infections. The roots, although less commonly used, have been associated with emetic and purgative properties.

Fruits and Seeds

The sweet, tangy pulp surrounding the seeds is consumed as a fruit and is used to relieve digestive complaints. In Mexico and parts of India, the fruit pulp is eaten to alleviate stomach discomfort and is believed to have mild laxative effects. The seeds are also consumed after roasting and are considered nutritious**.**

Ethnomedicinal Use for Ocular Conditions

Although less documented in mainstream literature, there are records in traditional Indian and Central American medicine of P. dulce leaves being used to treat eye infections and irritation. Tribal communities have used aqueous extracts or poultices made from fresh leaves to alleviate conjunctival redness, itching, and discharge. These traditional uses point toward antimicrobial and soothing properties that are now being investigated in modern pharmacological studies.

For instance, in some rural Indian settings, leaf juice is applied directly to inflamed eyes or mixed with rose water for enhanced soothing effects. While such practices are anecdotal, they offer an important lead for phytopharmacological studies into ocular formulations.

Nutritional and Functional Properties

The plant also offers nutritional benefits, particularly from its fruit pulp and seeds, which are rich in carbohydrates, proteins, and micronutrients such as calcium and iron. Additionally, antioxidant activity has been reported in both fruits and leaves, which could play a role in mitigating oxidative stress-related damage in ocular tissues—a potential link to its therapeutic relevance for eye infections and inflammation.[7]

Phytopharmacological Validation and Knowledge Gaps

While the traditional uses of P. dulce are well-documented ethnobotanically, only limited scientific studies have focused on its ocular applications. Preliminary phytochemical screenings reveal that the leaves contain a range of secondary metabolites with known antimicrobial and anti-inflammatory effects, such as flavonoids (quercetin, kaempferol), tannins, saponins, and phenolic acids.

These findings are encouraging, particularly given the need for new, natural agents to combat antibiotic-resistant ocular pathogens. However, there remains a significant knowledge gap regarding:

- Standardization of extracts
- Identification of active constituents targeting ocular pathogens
- Mechanistic studies on the mode of antimicrobial action
- Preclinical and clinical safety data for ophthalmic use

Conservation and Sustainable Use

Given its increasing importance in traditional medicine and potential in modern phytotherapy, the sustainable cultivation and harvesting of P. dulce should be prioritized. Overharvesting of leaves or bark may threaten wild populations if not managed properly. Agroforestry initiatives, community awareness programs, and scientific cultivation practices can help ensure its conservation while supporting traditional knowledge systems.

Ocular Infections: An Overview

Ocular infections are a significant cause of global morbidity and, in severe cases, permanent visual impairment or blindness. They affect individuals across all age groups and can originate from bacterial, viral, fungal, or parasitic pathogens. These infections may involve various anatomical parts of the eye, including the conjunctiva, cornea, eyelids, and intraocular structures. With the increasing prevalence of antimicrobial resistance and the emergence of opportunistic infections, the need for effective, safe, and affordable ocular therapeutics is more urgent than ever. This section presents an overview of the types of ocular infections, their etiological agents, common clinical presentations, current therapeutic challenges, and the growing necessity for plant-based antimicrobials like those from Pithecellobium dulce.[8]

Antimicrobial Activity of Pithecellobium dulce Leaves Against Ocular Pathogens

The antimicrobial potential of Pithecellobium dulce leaves has gained increasing attention in recent years, especially with the growing concern over antibiotic-resistant ocular pathogens. While this tropical plant has been widely used in folk medicine for treating infections, recent scientific investigations have provided compelling evidence supporting its use against a range of pathogenic microorganisms, including those implicated in ocular diseases.

Spectrum of Activity

Extracts of P. dulce leaves, particularly those prepared using ethanol and methanol, have shown broad-spectrum antimicrobial effects against Gram-positive and Gram-negative bacteria, as well as some fungi. Studies have reported inhibition of clinical isolates such as:

- **Gram-positive bacteria**: Staphylococcus aureus, Streptococcus pneumoniae
- **Gram-negative bacteria**: Pseudomonas aeruginosa, Escherichia coli, Klebsiella pneumoniae
- **Fungi**: Candida albicans, Aspergillus niger

These organisms are common culprits in ocular infections, including conjunctivitis, blepharitis, keratitis, and endophthalmitis.

Mechanisms of Antimicrobial Action

The antimicrobial activity of P. dulce leaf extracts is attributed to its rich composition of phytochemicals such as flavonoids (e.g., quercetin, kaempferol), tannins, phenolic acids, alkaloids, and saponins. These bioactive compounds exert their effects through multiple mechanisms:

- **Disruption of microbial cell membranes**: Saponins and flavonoids destabilize lipid bilayers, increasing permeability and leading to cell lysis.
- **Inhibition of enzyme activity**: Tannins bind to microbial proteins, including enzymes critical for replication and metabolism.
- **DNA intercalation**: Flavonoids like quercetin intercalate into microbial DNA, interfering with transcription and replication.
- **Antioxidant-mediated damage**: Phenolic acids reduce oxidative stress, enhancing the immune response and weakening pathogen defenses.

Such multimodal action decreases the likelihood of resistance development, making P. dulce extracts an attractive alternative to monotherapeutic antibiotics.[9]

In Vitro Studies Relevant to Ophthalmology

Preliminary in vitro studies using agar well diffusion and broth microdilution methods have demonstrated significant zones of inhibition for P. dulce extracts against S. aureus and P. aeruginosa, two of the most commonly isolated pathogens in bacterial conjunctivitis and keratitis. Minimum inhibitory concentration (MIC) values ranged between 100–400 µg/mL, depending on the solvent used and bacterial strain tested. Although no large-scale in vivo or clinical ophthalmic trials have yet been conducted, the antibacterial activity observed in vitro aligns with traditional claims of using the leaf juice or decoctions for treating eye infections in rural communities of India and Central America.[10]

Formulation Strategies for Ophthalmic Delivery

Formulating phytochemical-rich plant extracts like those from Pithecellobium dulce leaves into effective ophthalmic delivery systems requires a thoughtful approach that balances therapeutic efficacy, patient comfort, and ocular bioavailability. The eye presents several physiological barriers—such as tear turnover, blinking, and corneal impermeability—that

reduce the residence time and absorption of topically applied drugs. Hence, the development of advanced and biocompatible delivery systems is crucial for optimizing the therapeutic potential of P. dulce extracts in eye care.[11]

Conventional Formulations

The simplest method of administering P. dulce extracts for ocular infections is through **eye drops or aqueous solutions**, typically prepared from ethanol or aqueous extracts. However, these are rapidly cleared from the eye surface and often require frequent administration. To improve efficacy, **isotonic and pH-balanced formulations** (ideally pH 6.5–7.5) are essential to match the ocular environment and minimize irritation. **Sterility** is another critical factor; formulations must be filtered or autoclaved and packaged in sterile containers.

Advanced Ophthalmic Carriers

Recent innovations in drug delivery offer enhanced methods for sustained and targeted ocular delivery of plant-based antimicrobials:

- **Ophthalmic Gels**: Carbopol-based or HPMC (hydroxypropyl methylcellulose) gels can incorporate P. dulce extracts to provide prolonged contact time with the corneal surface, improving bioavailability and reducing dosing frequency.
- **In Situ Gelling Systems**: These liquid formulations undergo sol-to-gel transition upon contact with the eye due to temperature or pH changes, enabling sustained release of phytoconstituents.
- **Nanoparticles and Nanoemulsions**: Encapsulating P. dulce bioactives into biodegradable nanoparticles (e.g., chitosan, PLGA) enhances corneal penetration, protects against degradation, and allows controlled release.
- **Ocular Inserts or Films**: Plant extract-loaded inserts placed in the conjunctival sac can release actives over extended periods, though patient compliance may be lower

Safety, Toxicity, and Biocompatibility Considerations

When developing plant-based ophthalmic formulations, safety and biocompatibility are of paramount importance due to the sensitivity of ocular tissues and the potential for irritation or adverse reactions. While Pithecellobium dulce has a history of traditional use and several pharmacological properties, its safety profile for ocular application requires careful assessment through both preclinical and clinical studies.[12]

General Toxicological Profile

Studies on P. dulce have demonstrated that various parts of the plant, including the leaves, exhibit low systemic toxicity. Oral acute toxicity tests in rodent models using ethanolic or aqueous leaf extracts have shown no mortality or major adverse effects up to doses of 2000 mg/kg. Histopathological evaluations of major organs revealed no signs of damage, suggesting a wide safety margin for systemic use. However, systemic safety does not directly translate to ocular safety. The eye's unique anatomy and physiology necessitate specific evaluations for ocular irritation, toxicity, and compatibility.

Ocular Irritation and Compatibility

Very limited direct studies have been conducted on the ocular application of P. dulce extracts. Nevertheless, preliminary investigations using herbal formulations incorporating P. dulce have shown low ocular irritation in rabbit models based on Draize tests. Extracts diluted to safe concentrations (typically ≤1% w/v) were non-irritating, with no signs of conjunctival redness, tearing, or corneal damage.

Key considerations for ocular compatibility include:

- **Isotonicity** to prevent discomfort or corneal swelling
- **Neutral to slightly alkaline pH (6.5–7.5)** to match tear fluid
- **Absence of particulate matter** to avoid mechanical irritation
- **Preservative-free formulations** or those with natural stabilizers to reduce hypersensitivity

Phototoxicity and Allergenicity

Flavonoids and tannins, while beneficial, may cause phototoxic effects at high concentrations or prolonged exposure. Hence, formulation optimization must balance efficacy with safety. Additionally, allergic reactions, though rare, may occur in sensitive individuals and should be assessed in patch tests or skin sensitization models.

Challenges and Future Perspectives

The use of Pithecellobium dulce leaf extracts in ocular therapeutics presents an innovative and promising strategy for managing eye infections. However, translating this potential into a clinically viable ophthalmic product involves several challenges. These hurdles span from pharmacognostic standardization to formulation development, safety validation, and regulatory approval. At the same time, future research and technological advancements hold

the promise of addressing these limitations, enabling the development of safe, effective, and sustainable plant-based eye care solutions.[13]

Key Challenges

Lack of Standardization

One of the major limitations in using P. dulce extracts lies in the **variability of phytochemical content** due to differences in geography, climate, harvesting time, and extraction techniques. This inconsistency affects the reproducibility and efficacy of the formulations. Standardized extraction protocols, validated markers (e.g., quercetin, gallic acid), and consistent phytochemical profiling are essential to ensure batch-to-batch uniformity.

Limited Ocular-Specific Research

Most of the available studies on P. dulce focus on its general antimicrobial or anti-inflammatory effects. However, there is a **paucity of dedicated ophthalmic research**, particularly in vivo studies or clinical trials targeting eye infections. Moreover, the exact pharmacokinetics, ocular permeability, and metabolism of its active compounds in ocular tissues remain unknown**.**

Formulation Complexity

Designing stable and effective ophthalmic formulations for plant extracts poses formulation challenges:

- Low water solubility of certain phytochemicals
- Light and heat sensitivity of flavonoids
- Need for preservative-free, pH-balanced, and isotonic formulations

Furthermore, achieving prolonged ocular retention and optimal drug delivery without causing irritation requires innovative delivery systems such as **in situ gels**, **nanoparticles**, or **mucoadhesive inserts**, which require further research and validation.[14]

Regulatory and Clinical Barriers

Herbal ophthalmic products face **regulatory uncertainty**, as guidelines for plant-based eye formulations are not as well defined as those for synthetic drugs. Clinical trials to prove safety and efficacy, though essential, are resource-intensive and often overlooked in academic herbal research.[15]

Future Perspectives

Despite these challenges, the future for P. dulce-based ocular therapy is promising. Key future directions include:

- **Molecular docking and computational studies** to identify target-specific phytochemicals against ocular pathogens.
- **In vivo animal models** for conjunctivitis, keratitis, or dry eye syndrome to test the therapeutic efficacy of extracts.
- **Green extraction techniques** (e.g., supercritical fluid extraction) to obtain high-yield, solvent-free bioactives.
- **Integration with nanocarriers** like liposomes, niosomes, and chitosan nanoparticles for sustained drug delivery.
- **Collaborative studies** between ethnobotanists, ophthalmologists, pharmacologists, and formulation scientists to bridge traditional knowledge with modern pharmaceutical science.

CONCLUSION

Pithecellobium dulce leaves possess significant ocular antimicrobial potential, supported by their rich phytochemical profile, including flavonoids, tannins, and phenolic acids. Traditional uses, combined with emerging scientific evidence, highlight their promise in managing eye infections, especially amidst rising antibiotic resistance. Though preclinical studies are encouraging, challenges such as standardization, formulation, and clinical validation remain. With continued interdisciplinary research and innovation in ocular drug delivery, P. dulce could emerge as a natural, effective, and sustainable alternative in ophthalmic care, bridging traditional herbal wisdom with modern therapeutics.

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