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Polyherbal Anti-inflammatory Gels: A Comprehensive Review on the Phytochemistry, Pharmacological Activities, Formulation Strategies, and Therapeutic Potential of *Melia azedarach* and *Eucalyptus globulus.*

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Abstract: *Inflammation is a complex physiological response initiated by the immune system following tissue injury, microbial infection, or exposure to harmful stimuli. Although inflammation is essential for tissue repair and host defense, prolonged or uncontrolled inflammatory responses contribute to numerous chronic disorders including rheumatoid arthritis, osteoarthritis, dermatitis, psoriasis, diabetes, cardiovascular diseases, and neurodegenerative disorders. Conventional anti-inflammatory drugs such as non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids remain the primary therapeutic options; however, their prolonged use is frequently associated with gastrointestinal irritation, renal toxicity, cardiovascular complications, and immunosuppression. These limitations have encouraged researchers to investigate safer and more effective alternatives from medicinal plants.*

Polyherbal topical gels have emerged as an attractive drug delivery system because they combine the pharmacological benefits of multiple medicinal plants with the advantages of topical administration. Among medicinal plants, Melia azedarach (Chinaberry) and Eucalyptus globulus have received considerable scientific attention owing to their anti-inflammatory, antioxidant, antimicrobial, analgesic, and wound-healing activities. The bioactive constituents present in these plants, including limonoids, flavonoids, terpenoids, tannins, phenolic compounds, and eucalyptol, modulate various inflammatory pathways by suppressing cyclooxygenase enzymes, inflammatory cytokines, oxidative stress, and leukocyte infiltration.

Topical gel formulations prepared using these herbal extracts provide localized drug delivery directly to inflamed tissues while avoiding hepatic first-pass metabolism and minimizing systemic adverse effects. Modern pharmaceutical research has demonstrated that optimized polyherbal gels possess excellent spreadability, acceptable viscosity, suitable skin pH, improved patient compliance, prolonged residence time, and enhanced therapeutic efficacy.

This review critically summarizes the current scientific literature regarding inflammation, topical drug delivery systems, phytochemistry, pharmacological activities, formulation strategies, evaluation methods, and recent advances related to polyherbal anti-inflammatory gels containing Melia azedarach and Eucalyptus globulus. The review also highlights existing research gaps and future opportunities for the development of standardized, evidence-based herbal topical formulations.

Keywords: Polyherbal Gel, Anti-inflammatory, Topical Drug Delivery, *Melia azedarach*, *Eucalyptus globulus,* Herbal Medicine

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I. INTRODUCTION

Inflammation is a highly coordinated biological response that protects the body against harmful stimuli including microbial invasion, chemical irritants, physical injury, and tissue damage. It represents one of the most fundamental defense mechanisms of the immune system and is essential for maintaining tissue homeostasis. During inflammation, immune cells migrate toward the injured tissue, inflammatory mediators are released, damaged cells are eliminated, and tissue repair is initiated. Although inflammation is beneficial during the early stages of injury, persistent or uncontrolled inflammatory responses may lead to chronic diseases associated with progressive tissue destruction.

Inflammatory disorders remain among the leading causes of disability worldwide. Conditions such as rheumatoid arthritis, osteoarthritis, psoriasis, dermatitis, tendinitis, muscular pain, inflammatory bowel disease, diabetes-associated inflammation, and cardiovascular diseases are directly or indirectly linked with prolonged inflammatory responses. According to the World Health Organization, chronic inflammatory diseases contribute significantly to global morbidity and healthcare expenditure.

Current management of inflammatory diseases primarily depends on NSAIDs and corticosteroids. NSAIDs reduce inflammation by inhibiting cyclooxygenase enzymes (COX-1 and COX-2), thereby decreasing prostaglandin synthesis. Corticosteroids suppress immune responses by inhibiting inflammatory gene expression. Despite their effectiveness, prolonged administration of these drugs is associated with gastric ulceration, gastrointestinal bleeding, renal impairment, hepatotoxicity, hypertension, cardiovascular complications, osteoporosis, adrenal suppression, and increased susceptibility to infections.

These limitations have accelerated research into herbal medicines. Medicinal plants have served as therapeutic agents for centuries because they contain numerous bioactive phytochemicals capable of modulating inflammatory pathways with comparatively fewer adverse effects. Herbal medicines also possess antioxidant, antimicrobial, analgesic, immunomodulatory, and wound-healing activities that contribute to comprehensive management of inflammatory disorders.

Polyherbal formulations represent an advanced approach in herbal medicine by combining two or more medicinal plants within a single dosage form. The concept is based on synergism, where multiple phytochemicals act simultaneously on different biological targets to improve therapeutic efficacy while reducing toxicity.

Among various dosage forms, topical gels have become increasingly important because they deliver active constituents directly to the affected site. Topical administration minimizes systemic exposure, bypasses hepatic first-pass metabolism, reduces gastrointestinal side effects, improves patient compliance, and allows controlled drug release. Gels are generally non-greasy, easily washable, aesthetically acceptable, and suitable for long-term treatment.

Among medicinal plants investigated for topical formulations, Melia azedarach (Chinaberry) and Eucalyptus globulus possess remarkable therapeutic potential.

Melia azedarach contains limonoids, triterpenoids, flavonoids, tannins, saponins, steroids, and phenolic compounds responsible for anti-inflammatory, antimicrobial, antioxidant, analgesic, antiparasitic, and wound-healing activities. Experimental studies demonstrate that these constituents suppress inflammatory mediators including TNF-α, IL-1β, IL-6, prostaglandins, and nitric oxide.

Similarly, Eucalyptus globulus contains essential oils rich in 1,8-cineole (eucalyptol), α-pinene, limonene, flavonoids, tannins, and phenolic acids. These compounds inhibit oxidative stress, stabilize cellular membranes, reduce cytokine production, and suppress inflammatory enzyme activity.

Combining these medicinal plants within a topical gel formulation offers several advantages including broader pharmacological activity, enhanced antimicrobial protection, improved antioxidant capacity, superior wound-healing potential, and synergistic inhibition of inflammatory pathways.

Recent pharmaceutical research has therefore focused on developing standardized polyherbal gels with improved stability, enhanced skin penetration, prolonged drug release, and better therapeutic outcomes. Modern excipients such as Carbopol, hydroxypropyl methylcellulose (HPMC), propylene glycol, polyethylene glycol, and natural polymers further improve formulation characteristics including viscosity, spreadability, adhesion, and stability.

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This review critically discusses the available literature concerning inflammation, topical drug delivery systems, phytochemistry of Melia azedarach and Eucalyptus globulus, formulation strategies, evaluation methods, recent scientific advances, and future prospects for polyherbal anti-inflammatory gels.

Inflammation and Pathophysiology:

1. Definition of Inflammation:

Inflammation is a protective biological response initiated by vascular tissues and immune cells following exposure to harmful stimuli including pathogens, damaged cells, toxins, allergens, chemicals, radiation, and physical trauma. The primary objective of inflammation is to eliminate the causative agent, remove damaged tissue, and initiate repair mechanisms that restore normal physiological function.

The inflammatory response involves coordinated activation of blood vessels, leukocytes, cytokines, chemokines, complement proteins, and inflammatory enzymes. These mediators interact through complex signaling pathways that regulate vascular permeability, immune cell recruitment, oxidative stress, and tissue remodeling.

While acute inflammation is generally beneficial and self-limiting, chronic inflammation becomes pathological when inflammatory mediators remain continuously activated, resulting in tissue destruction and disease progression.

2. Classical Signs of Inflammation:

The classical clinical manifestations include:

- Redness (Rubor): Due to vasodilation and increased blood flow.
- Heat (Calor): Caused by enhanced local blood circulation.
- Swelling (Tumor): Resulting from increased vascular permeability and fluid accumulation.
- Pain (Dolor): Produced by inflammatory mediators stimulating sensory nerve endings.
- Loss of Function (Functio Laesa): Due to pain, edema, and tissue damage.

3. Types of Inflammation:

i. Acute Inflammation

- Rapid onset
- Short duration
- Dominated by neutrophils
- Usually resolves completely

ii. Chronic Inflammation

- Long-lasting
- Dominated by macrophages and lymphocytes
- Leads to fibrosis and tissue destruction

iii. Localized Inflammation

Restricted to a particular tissue or organ.

iv. Systemic Inflammation

Affects multiple organs and may produce fever, fatigue, leukocytosis, and elevated inflammatory markers.

4. Pathophysiology of Inflammation:

The inflammatory response progresses through several sequential stages:

1. Recognition of tissue injury
2. Activation of resident macrophages and mast cells

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3. Release of histamine, serotonin, prostaglandins, leukotrienes, TNF-α, IL-1β, and IL-6
4. Vasodilation
5. Increased vascular permeability
6. Leukocyte adhesion and migration
7. Phagocytosis
8. Tissue repair and remodeling

Major inflammatory signaling pathways include:
• NF-κB pathway
• MAPK pathway
• COX pathway
• LOX pathway
• JAK/STAT pathway

5. Cellular and Molecular Mechanism of Inflammation:
Inflammation is a tightly regulated biological process involving interactions between immune cells, vascular endothelial cells, inflammatory mediators, and intracellular signaling pathways. Following tissue injury or infection, resident immune cells detect harmful stimuli through pattern recognition receptors (PRRs), particularly Toll-like receptors (TLRs). These receptors recognize pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs), initiating a cascade of inflammatory events.
Activated macrophages and mast cells release histamine, prostaglandins, leukotrienes, nitric oxide, tumor necrosis factor-alpha (TNF-α), interleukins (IL-1β, IL-6), and chemokines. These mediators increase vascular permeability, recruit leukocytes to the injured tissue, promote phagocytosis, and stimulate tissue repair.
If the inflammatory response is not properly regulated, continuous cytokine production results in chronic inflammation characterized by fibrosis, tissue degeneration, oxidative stress, and organ dysfunction.

6. Phases of Inlammation:
Inflammation progresses through three major phases.

1. Vascular Phase
Immediately after tissue injury, blood vessels undergo transient vasoconstriction followed by prolonged vasodilation.
Major events include:
• Vasodilation
• Increased blood flow
• Increased capillary permeability
• Plasma protein leakage
• Formation of inflammatory exudate
These changes produce the classical signs of redness, warmth, and swelling.

2. Cellular Phase
White blood cells migrate toward the injured tissue through a process called leukocyte extravasation.
The sequence includes:
• Margination
• Rolling
• Adhesion
• Diapedesis

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• Chemotaxis
• Phagocytosis

3. Resolution Phase

Successful inflammation ends with removal of inflammatory mediators and tissue repair. Major events include:

• Clearance of apoptotic neutrophils
• Macrophage-mediated phagocytosis
• Fibroblast proliferation
• Collagen synthesis
• Angiogenesis
• Tissue remodeling

Failure of resolution contributes to chronic inflammatory diseases.

7. Major Chemical Mediators of Inflammation:

Mediator	Source	Biological Function
Histamine	Mast cells	Vasodilation, vascular permeability
Serotonin	Platelets	Vasodilation
Bradykinin	Plasma proteins	Pain, vasodilation
Prostaglandins	Arachidonic acid	Pain, fever, inflammation
Leukotrienes	Leukocytes	Chemotaxis, bronchoconstriction
Nitric Oxide	Macrophages	Vasodilation
TNF-α	Macrophages	Cytokine activation
IL-1β	Macrophages	Fever, inflammation
IL-6	Macrophages	Acute phase protein synthesis
Chemokines	Leukocytes	Leukocyte recruitment

8. Role of Oxidative Stress in Inflammation:

Reactive oxygen species (ROS) are continuously generated during inflammatory responses. Major ROS include:

• Superoxide radical
• Hydroxyl radical
• Hydrogen peroxide
• Peroxynitrite

Although ROS destroy invading microorganisms, excessive ROS production damages cellular proteins, DNA, lipids, and mitochondria.

Oxidative stress activates NF-κB signaling, leading to increased production of inflammatory cytokines and progression of chronic inflammatory diseases.

9. Cytokines Involved in Inflammation:

Cytokines regulate communication between immune cells.

1) Pro-inflammatory Cytokines

• TNF-α
• IL-1β
• IL-6
• IL-8

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• IFN-γ Functions:
• Recruit leukocytes
• Promote fever
• Increase vascular permeability
• Stimulate prostaglandin synthesis
• Activate macrophages

2) Anti-inflammatory Cytokines
• IL-10
• TGF-β
• IL-4
• IL-13

Functions:
• Suppress inflammatory mediator production
• Promote tissue repair
• Limit immune cell activation
• Restore tissue homeostasis

10. Inflammatory Signaling Pathways:
A. Cyclooxygenase (COX) Pathway: Cyclooxygenase enzymes convert arachidonic acid into prostaglandins.
COX-1
• Constitutive enzyme
• Gastric protection
• Platelet aggregation

COX-2
• Inducible enzyme
• Activated during inflammation
• Responsible for pain and swelling

NSAIDs inhibit COX enzymes but may cause gastric ulceration and renal toxicity.

B. Lipoxygenase (LOX) Pathway: LOX converts arachidonic acid into leukotrienes.
Leukotrienes promote:
• Bronchoconstriction
• Chemotaxis
• Vascular permeability
• Chronic inflammation
Several herbal constituents exhibit dual COX and LOX inhibitory activity.

C. MAPK Pathway: Mitogen-Activated Protein Kinase regulates:
• Cytokine production
• Cell proliferation
• Apoptosis
• Oxidative stress

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Suppression of MAPK signaling reduces inflammation.

11. Need for Herbal Anti-inflammatory Therapy:

The increasing prevalence of chronic inflammatory diseases has renewed interest in medicinal plants as safer therapeutic alternatives.

Herbal medicines offer several advantages:

- Lower incidence of adverse effects
- Multiple mechanisms of action
- Antioxidant activity
- Antimicrobial activity
- Improved patient acceptance
- Cost-effectiveness
- Suitable for long-term therapy

Medicinal plants such as Melia azedarach and Eucalyptus globulus contain diverse phytochemicals capable of simultaneously inhibiting inflammatory cytokines, oxidative stress, prostaglandin synthesis, and microbial infections.

Their incorporation into topical gel formulations provides localized treatment with minimal systemic toxicity, making polyherbal gels a promising strategy for managing inflammatory disorders.

TOPICAL DRUG DELIVERY SYSTEM:

1. Introduction:

Topical drug delivery refers to the application of pharmaceutical formulations directly onto the skin or mucosal surfaces to produce localized therapeutic effects at or near the site of application. It is one of the oldest and most widely accepted routes of drug administration due to its convenience, ease of application, and ability to provide targeted treatment. Unlike oral dosage forms, topical formulations bypass the gastrointestinal tract and hepatic first-pass metabolism, thereby reducing systemic exposure and minimizing adverse effects.

Topical drug delivery systems (TDDS) have gained significant importance in modern pharmaceutical science because they allow direct application of drugs to inflamed or infected tissues. This localized delivery improves therapeutic efficacy while decreasing the dose required to achieve the desired pharmacological response.

The development of herbal topical formulations has further expanded the scope of topical therapy. Medicinal plants rich in flavonoids, terpenoids, alkaloids, tannins, phenolic compounds, and essential oils are increasingly incorporated into gels, creams, ointments, lotions, and patches for treating inflammatory disorders, wound infections, burns, fungal infections, and musculoskeletal pain.

Polyherbal anti-inflammatory gels containing Melia azedarach and Eucalyptus globulus combine the advantages of topical drug delivery with the synergistic pharmacological activities of medicinal plants. These formulations provide sustained drug release, improved patient compliance, enhanced skin compatibility, and reduced systemic toxicity.

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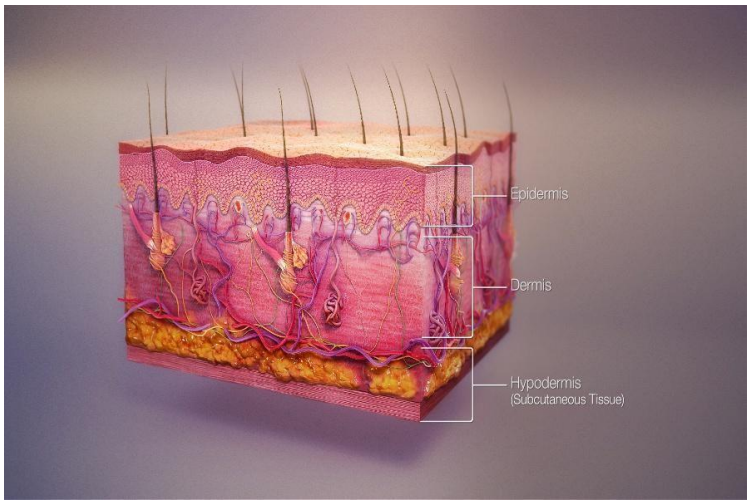

2. Human Skin

Human skin is the largest organ of the body and forms the primary protective barrier between the internal organs and the external environment. In adults, the skin covers approximately 1.5–
2.0 m² and constitutes nearly 15–16% of total body weight. Besides acting as a physical barrier, it performs numerous physiological, immunological, sensory, and metabolic functions essential for maintaining homeostasis.

The skin regulates body temperature, prevents excessive water loss, protects against microbial invasion, detects environmental stimuli, synthesizes vitamin D, and participates in immune surveillance. These unique characteristics make the skin an attractive route for localized drug delivery.

2. Structure of Human Skin:

The skin consists of three major layers:

1. Epidermis

The epidermis is the outermost layer of the skin.

It is composed primarily of keratinized epithelial cells arranged into five sublayers:

- Stratum corneum
- Stratum lucidum
- Stratum granulosum
- Stratum spinosum
- Stratum basale

Among these layers, the stratum corneum serves as the principal barrier to drug penetration. It consists of dead keratin-filled cells embedded in a lipid matrix that limits the diffusion of most pharmaceutical compounds.

Functions of the epidermis include:

- Protection against pathogens
- Prevention of water loss
- UV protection
- Formation of keratin
- Pigmentation through melanocytes

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2. Dermis

The dermis lies beneath the epidermis and consists of connective tissue rich in collagen and elastin fibers.

It contains:

- Blood vessels
- Lymphatic vessels
- Hair follicles
- Sweat glands
- Sebaceous glands
- Sensory nerve endings
- Fibroblasts

The dermis provides mechanical strength, elasticity, and nourishment to the epidermis. Drugs reaching the dermis may enter systemic circulation through dermal blood vessels.

3. Hypodermis (Subcutaneous Tissue)

The hypodermis consists mainly of adipose tissue and loose connective tissue. Functions include:

- Thermal insulation
- Mechanical cushioning
- Energy storage
- Protection against trauma

Although topical formulations generally do not target this layer, highly permeable drugs may diffuse into deeper tissues.

4 Functions of Human Skin:

The major physiological functions include:

Protective Function:

Protects the body against microorganisms, chemicals, ultraviolet radiation, and physical injury.

Regulation of Body Temperature:

Maintains body temperature through sweating and regulation of blood flow.

5. Routes of Drug Penetration Through Skin:

Drugs penetrate the skin through three principal pathways.

A. Intercellular Route:

Drug molecules diffuse between corneocytes through lipid-rich extracellular spaces. Characteristics:

- Major pathway for lipophilic drugs
- Slow diffusion
- Most common penetration route

B. Transcellular Route:

Drug molecules pass directly through keratinized cells. Characteristics:

- Suitable for both hydrophilic and lipophilic drugs
- Requires repeated partitioning between aqueous and lipid phases

C. Transappendageal Route:

Drug molecules penetrate through:

- Hair follicles
- Sweat glands

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• Sebaceous glands

Although this pathway accounts for a small surface area, it is important for large molecules and nanoparticles.

6. Gels as Topical Drug Delivery Systems:

A gel is a semisolid pharmaceutical dosage form in which liquid is immobilized within a three-dimensional polymeric network.

An ideal topical gel should possess:

• Appropriate viscosity
• Good spreadability
• Homogeneous appearance
• Acceptable pH
• High stability
• Easy washability
• Non-irritating nature
• Controlled drug release
• Good patient compliance Common gelling agents include:
• Carbopol 934
• Carbopol 940
• Hydroxypropyl methylcellulose (HPMC)
• Sodium alginate
• Xanthan gum
• Chitosan

7. Applications of Topical Drug Delivery:

Topical formulations are extensively used for treating:

• Arthritis
• Osteoarthritis
• Rheumatoid arthritis
• Muscular pain
• Sports injuries
• Tendinitis

HERBAL GELS AND POLYHERBAL GELS:

Herbal medicines have been used for thousands of years as primary therapeutic agents for the prevention and treatment of various diseases. According to the World Health Organization (WHO), nearly 80% of the world's population depends partly on medicinal plants for primary healthcare. The growing awareness regarding the adverse effects of synthetic drugs has accelerated the development of herbal pharmaceutical formulations, particularly for chronic inflammatory disorders.

Among various topical dosage forms, herbal gels have attracted considerable attention because they provide localized drug delivery, improved patient compliance, reduced systemic toxicity, and enhanced therapeutic efficacy. Herbal gels incorporate extracts or essential oils obtained from medicinal plants into a suitable gel base, allowing the controlled release of bioactive constituents directly at the affected site.

Polyherbal gels are a further advancement of herbal formulations in which two or more medicinal plant extracts are combined to achieve synergistic pharmacological effects. Such formulations have demonstrated superior anti-inflammatory, analgesic, antioxidant, antimicrobial, and wound-healing activities compared with single-herb preparations.

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The combination of Melia azedarach and Eucalyptus globulus represents a promising polyherbal formulation because both plants possess complementary phytochemicals that target multiple inflammatory pathways simultaneously.

Herbal Gel:

A herbal gel is a semisolid pharmaceutical dosage form prepared by incorporating one or more medicinal plant extracts or essential oils into a hydrophilic polymeric base. The gel acts as a carrier that facilitates controlled release of herbal constituents onto the skin surface while maintaining prolonged contact with the affected tissue.

Unlike ointments, herbal gels are non-greasy, transparent, aesthetically acceptable, easily washable, and rapidly absorbed through the skin. These properties improve patient compliance, particularly during long-term therapy.

Herbal gels are widely used for the management of:

- Inflammation
- Arthritis
- Muscle pain
- Sports injuries
- Burns
- Wound healing
- Acne
- Dermatitis
- Fungal infections
- Psoriasis

Polyherbal Concept:

Polyherbalism refers to the use of multiple medicinal plants in a single pharmaceutical formulation. This concept has been extensively practiced in Ayurveda, Siddha, and Traditional Chinese Medicine.

The rationale behind polyherbal formulations is that different phytochemicals act through multiple mechanisms, producing synergistic therapeutic effects while reducing toxicity.

Compared with single-herb formulations, polyherbal preparations often exhibit:

- Greater therapeutic efficacy
- Broader pharmacological spectrum
- Improved antioxidant activity
- Enhanced antimicrobial action
- Better anti-inflammatory response
- Reduced adverse effects

Principle of Polyherbal Synergism:

The therapeutic superiority of polyherbal formulations is primarily attributed to synergism. Synergism may occur through several mechanisms.

Pharmacodynamic Synergism:

Different phytochemicals act on different inflammatory pathways simultaneously. Example:

- Flavonoids inhibit cytokine production.
- Terpenoids suppress prostaglandin synthesis.
- Phenolic compounds reduce oxidative stress.

Together, they produce stronger anti-inflammatory activity.

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Pharmacokinetic Synergism:
One herbal constituent enhances the absorption, distribution, metabolism, or retention of another constituent. This increases overall therapeutic efficacy.

Protective Synergism:
Certain phytochemicals protect other bioactive compounds against degradation or oxidation, thereby improving formulation stability.

Why Polyherbal Gels are Superior to Single Herbal Gels:

Single Herbal Gel	Polyherbal Gel
Single active constituent	Multiple active constituents
Limited mechanism	Multiple mechanisms
Lower efficacy	Higher efficacy
Narrow spectrum	Broad-spectrum activity
Less antioxidant potential	Greater antioxidant activity
Limited antimicrobial activity	Enhanced antimicrobial activity
Less wound healing	Better wound healing

Phytochemicals Responsible for Anti-inflammatory Activity:
Medicinal plants contain numerous secondary metabolites responsible for therapeutic activity.

Phytochemical	Pharmacological Activity
Flavonoids	Anti-inflammatory, antioxidant
Phenolic compounds	Free radical scavenging
Terpenoids	COX inhibition
Alkaloids	Analgesic activity
Limonoids	Anti-inflammatory
Saponins	Immunomodulatory
Tannins	Astringent, wound healing
Steroids	Anti-inflammatory
Glycosides	Tissue protection

These phytochemicals collectively reduce inflammatory responses by suppressing oxidative stress and inflammatory mediators.

Melia azedarach (Chinaberry): Botanical Profile, Phytochemistry, and Pharmacological Activities.
Melia azedarach L., commonly known as Chinaberry, Persian lilac, Bakayan, or Mahanimba, belongs to the family Meliaceae. It is a medium-sized deciduous tree widely distributed in tropical and subtropical regions including India, China, Pakistan, Nepal, Sri Lanka, Australia, and South America. Traditionally, different parts of the plant such as leaves, bark, fruits, flowers, and seeds have been used in Ayurvedic, Unani, and Chinese medicine for treating fever, inflammation, skin disorders, intestinal worms, microbial infections, and wounds.

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Recent pharmacological studies have confirmed that Melia azedarach contains several biologically active phytochemicals responsible for anti-inflammatory, antioxidant, antimicrobial, analgesic, antiparasitic, and wound-healing activities. Because of these properties, the plant has gained considerable attention for developing herbal topical formulations, particularly polyherbal anti-inflammatory gels.

Taxonomical Classification:

Category	Classification
Kingdom	Plantae
Division	Magnoliophyta
Class	Magnoliopsida
Order	Sapindales
Family	Meliaceae
Genus	Melia
Species	Melia azedarach L.

Botanical Description:

Melia azedarach is a fast-growing deciduous tree reaching a height of 7-15 m. The bark is dark brown to gray with longitudinal fissures. Leaves are bipinnately compound, bright green, and aromatic when crushed. Flowers are pale violet to lavender in color and arranged in terminal panicles. Fruits are yellow spherical drupes containing hard seeds rich in limonoids. The plant grows well in warm climates and tolerates drought, making it widely available in tropical countries.

Phytochemical Constituents:

The therapeutic potential of Melia azedarach is mainly attributed to its diverse phytochemicals.

Limonoids:

- Toosendanin
- Meliatoxin
- Azedarachin
- Melianone
- Melianol

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Flavonoids:
• Quercetin
• Kaempferol
• Rutin
Flavonoids possess antioxidant and anti-inflammatory properties by scavenging free radicals and inhibiting inflammatory mediators.

Terpenoids:
Terpenoids reduce inflammatory responses by suppressing cyclooxygenase (COX) and lipoxygenase (LOX) pathways.

Phenolic Compounds:
Phenolic compounds neutralize reactive oxygen species and protect tissues from oxidative damage.

Other Constituents:
• Tannins
• Saponins
• Alkaloids
• Glycosides
• Steroids
• β-Sitosterol
• Stigmasterol

Pharmacological Activities:
Anti-inflammatory Activity: Extracts of Melia azedarach inhibit inflammatory mediators such as prostaglandins, nitric oxide, TNF-α, IL-1β, and IL-6. Limonoids and flavonoids suppress NF-κB activation, reducing edema, pain, and tissue inflammation.
Antioxidant Activity: Flavonoids and phenolic compounds effectively scavenge reactive oxygen species (ROS), reducing oxidative stress and preventing cellular damage.
Antimicrobial Activity: The plant exhibits broad-spectrum antibacterial and antifungal activity against pathogens such as Staphylococcus aureus, Escherichia coli, and Candida albicans, supporting its use in wound healing and topical formulations.
Analgesic Activity: Methanolic and ethanolic extracts have demonstrated significant analgesic effects in experimental models by reducing pain associated with inflammatory conditions.
Wound-Healing Activity: Bioactive constituents promote fibroblast proliferation, collagen deposition, angiogenesis, and epithelial regeneration, accelerating wound healing.
Antiparasitic Activity: Limonoids exhibit strong insecticidal and antiparasitic properties, making the plant useful in traditional medicine.

Mechanim of Anti-inflammatory Action:
The anti-inflammatory effect of Melia azedarach is mediated through:
• Inhibition of COX-2 enzyme
• Suppression of NF-κB signaling
• Reduction of TNF-α, IL-1β, and IL-6 production
• Decreased nitric oxide synthesis
• Inhibition of leukocyte infiltration
• Antioxidant scavenging of free radicals

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• Stabilization of lysosomal membranes
These mechanisms contribute to reduced pain, swelling, redness, and tissue damage.

Applications in Topical Formulations:
Due to its anti-inflammatory, antimicrobial, antioxidant, and wound-healing properties, Melia azedarach has been incorporated into:

• Herbal gels

Eucalyptus globulus: Botanical Profile, Phytochemistry, and Pharmacological Activities:

Eucalyptus globulus Labill., commonly known as Blue Gum, belongs to the family Myrtaceae. Native to Australia, it is widely cultivated in India, China, Brazil, Spain, and Portugal. The leaves are rich in essential oils, particularly 1,8-cineole (eucalyptol), which possesses potent anti-inflammatory, antimicrobial, antioxidant, and analgesic activities.
Eucalyptus oil has been extensively used in pharmaceutical, cosmetic, and aromatherapy products for treating respiratory disorders, muscular pain, wound infections, and inflammatory conditions.

Taxonomical Classification:

Category	Classification
Kingdom	Plantae
Division	Magnoliophyta
Class	Magnoliopsida
Order	Myrtales
Family	Myrtaceae
Genus	Eucalyptus
Species	Eucalyptus globulus Labill.

Botanical Description:
Eucalyptus globulus is an evergreen tree that can grow up to 70 meters under favorable conditions. The bark is smooth and grayish-white, while the leaves are lance-shaped, leathery, and aromatic due to abundant essential oil glands. The leaves are the principal medicinal part used for extraction of eucalyptus oil.

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Phytochemical Constituents:
Major phytochemicals include:

Essential Oils:
• 1,8-Cineole (Eucalyptol)
• α-Pinene
• β-Pinene
• Limonene
• Camphene

Flavonoids:
• Quercetin
• Rutin
• Catechin

Phenolic Compounds:
• Gallic acid
• Chlorogenic acid
• Caffeic acid

Other Constituents:
• Tannins
• Terpenoids
• Saponins

Pharmacological Activities:
Anti-inflammatory Activity: Eucalyptol inhibits COX-2 expression, NF-κB activation, and inflammatory cytokines, reducing edema and pain.
Antioxidant Activity: Flavonoids and phenolic compounds protect tissues from oxidative stress by neutralizing free radicals.
Antimicrobial Activity: Eucalyptus oil exhibits antibacterial, antiviral, and antifungal activity against a wide range of pathogens.
Analgesic Activity: Topical application reduces muscular pain and joint discomfort through anti-inflammatory and counter-irritant effects.
Wound-Healing Activity: Promotes tissue regeneration and prevents microbial infection in wounds.
Respiratory Benefits: Eucalyptol acts as an expectorant and mucolytic agent, improving airway clearance in respiratory disorders.

Mechanism of Anti-inflammatory Action:
The anti-inflammatory activity of Eucalyptus globulus involves:
• Suppression of NF-κB signaling
• Inhibition of COX-2 and prostaglandin synthesis
• Reduction of TNF-α, IL-1β, and IL-6
• Antioxidant activity
• Membrane stabilization
• Decreased leukocyte migration

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Pharmaceutical Applications:

Eucalyptus globulus is widely used in:

- Anti-inflammatory gels
- Pain-relief creams
- Ointments
- Mouthwashes
- Cough syrups
- Inhalation preparations
- Wound dressings
- Cosmetic products

Challenges and Future Perspectives:

Challenges in the Development of Polyherbal Anti-inflammatory Gels

Despite the increasing interest in herbal medicines, several scientific, pharmaceutical, and regulatory challenges limit the widespread acceptance and commercialization of polyherbal anti-inflammatory gels. Although medicinal plants such as Melia azedarach and Eucalyptus globulus possess promising pharmacological activities, ensuring consistent quality, safety, efficacy, and stability remains a significant concern.

1. Standardization of Herbal Raw Materials

One of the major challenges is the lack of standardization of medicinal plant materials. The phytochemical composition of herbal extracts varies depending on geographical location, climate, soil conditions, harvesting season, plant age, and extraction methods. Such variability can lead to inconsistent therapeutic efficacy and difficulties in maintaining batch-to-batch uniformity.

2. Phytochemical Variability

Medicinal plants contain numerous bioactive compounds whose concentrations fluctuate naturally. Variations in flavonoids, terpenoids, limonoids, phenolic compounds, and essential oils may significantly influence the anti-inflammatory activity of the final formulation. Advanced analytical techniques such as HPLC, GC-MS, LC-MS, and HPTLC are therefore essential for quality control.

3. Stability of Herbal Formulations

Many phytochemicals are sensitive to environmental factors such as temperature, humidity, oxygen, and light. Oxidation and degradation of essential oils and phenolic compounds may reduce therapeutic efficacy during storage. Appropriate packaging materials, antioxidants, and stability studies are therefore required to ensure product quality throughout its shelf life.

4. Skin Penetration and Bioavailability

The stratum corneum acts as a major barrier to drug penetration. Although topical gels provide localized therapy, achieving sufficient penetration of herbal bioactive compounds into deeper skin layers remains challenging. The incorporation of suitable penetration enhancers and novel drug delivery systems may improve skin permeability and therapeutic outcomes.

5. Safety and Toxicological Evaluation

Although herbal medicines are generally perceived as safe, some medicinal plants may cause skin irritation, allergic reactions, hypersensitivity, or toxicity when used improperly. Comprehensive toxicological studies, including acute,

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sub-chronic, chronic, dermal irritation, sensitization, and phototoxicity studies, are necessary before clinical application.

Future Perspectives:

Recent advances in pharmaceutical technology have created new opportunities for the development of highly effective polyherbal topical formulations. Future research should focus on improving formulation quality, therapeutic efficacy, and scientific validation.

1. Nano-Herbal Drug Delivery Systems

Nanoemulsions, liposomes, solid lipid nanoparticles, nanostructured lipid carriers, and polymeric nanoparticles can significantly improve skin penetration, bioavailability, controlled drug release, and stability of herbal bioactive compounds.

2. Advanced Polymer-Based Gels

The use of novel biodegradable and biocompatible polymers can enhance viscosity, adhesion, spreadability, drug release, and patient compliance. Smart hydrogels capable of responding to pH, temperature, or inflammatory conditions represent an emerging area of research.

3. Standardization of Herbal Extracts

Future formulations should employ standardized extracts containing known concentrations of active phytochemicals. Marker-based quality control using chromatographic techniques will improve consistency and reproducibility.

4. Clinical Evaluation

Large-scale randomized controlled clinical trials are required to establish the safety, efficacy, optimal dosage, and long-term therapeutic benefits of polyherbal anti-inflammatory gels in comparison with conventional anti-inflammatory drugs.

5. Mechanistic Studies

Further molecular studies are necessary to understand the interaction of phytochemicals with inflammatory signaling pathways such as NF-κB, MAPK, COX-2, LOX, JAK/STAT, and Nrf2. Such investigations may facilitate the discovery of novel therapeutic targets.

6. Sustainable Utilization of Medicinal Plants

Conservation, cultivation, and sustainable harvesting of medicinal plants are essential to ensure long-term availability of high-quality raw materials while protecting biodiversity and ecological balance.

7. Commercialization Potential

Growing consumer preference for natural and eco-friendly products offers significant commercial opportunities for polyherbal topical formulations. Pharmaceutical industries may focus on developing standardized, evidence-based herbal gels for the treatment of arthritis, sports injuries, dermatological disorders, and chronic inflammatory diseases.

II. CONCLUSION

Inflammation is a complex biological response that plays an essential role in host defense and tissue repair. However, persistent or uncontrolled inflammation contributes to the development of numerous chronic diseases, including arthritis, musculoskeletal disorders, dermatological conditions, and autoimmune diseases. Although conventional anti-inflammatory drugs such as NSAIDs and corticosteroids provide effective symptomatic relief, their long-term use is

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frequently associated with gastrointestinal, renal, cardiovascular, and immunological adverse effects. Consequently, there is growing interest in the development of safer and more effective alternatives derived from medicinal plants.

This review highlights the therapeutic potential of polyherbal anti-inflammatory gels as an effective topical drug delivery system. The combination of Melia azedarach and Eucalyptus globulus offers a synergistic approach by integrating multiple pharmacological activities, including anti-inflammatory, antioxidant, antimicrobial, analgesic, and wound-healing effects. These medicinal plants contain diverse bioactive constituents such as limonoids, flavonoids, terpenoids, phenolic compounds, tannins, and eucalyptol, which modulate inflammatory pathways by inhibiting cyclooxygenase enzymes, pro-inflammatory cytokines, oxidative stress, and nuclear factor-kappa B (NF-κB) signaling.

Topical gel formulations provide several pharmaceutical advantages, including localized drug delivery, avoidance of first-pass metabolism, improved patient compliance, reduced systemic toxicity, and enhanced therapeutic efficacy. Appropriate formulation strategies involving optimized polymers, penetration enhancers, preservatives, and standardized herbal extracts can further improve the quality and performance of polyherbal gels.

Despite encouraging preclinical evidence, challenges such as phytochemical variability, standardization, stability, regulatory approval, and limited clinical data continue to hinder the widespread clinical application of herbal topical formulations. Future research should therefore focus on advanced drug delivery systems, standardized extraction procedures, molecular pharmacology, toxicity evaluation, and well-designed clinical trials to establish their long-term safety and effectiveness.

In conclusion, polyherbal anti-inflammatory gels containing Melia azedarach and Eucalyptus globulus represent a promising and scientifically supported alternative to conventional topical anti-inflammatory therapies. With continued research, technological innovation, and rigorous clinical validation, these formulations have the potential to become valuable therapeutic options for the management of inflammatory and dermatological disorders while contributing to the growing field of evidence-based herbal medicine.

Results:

The literature reviewed demonstrates that polyherbal anti-inflammatory gels containing Melia azedarach and Eucalyptus globulus possess significant therapeutic potential for the management of localized inflammatory conditions. Published studies consistently report that both medicinal plants are rich sources of biologically active phytochemicals, including flavonoids, terpenoids, limonoids, tannins, phenolic compounds, and essential oils, which contribute to their anti-inflammatory, antioxidant, antimicrobial, analgesic, and wound-healing activities.

Experimental studies have shown that extracts of Melia azedarach effectively inhibit the production of inflammatory mediators such as tumor necrosis factor-alpha (TNF-α), interleukin-1β (IL-1β), interleukin-6 (IL-6), prostaglandins, and nitric oxide. These effects are primarily attributed to the presence of limonoids, flavonoids, and triterpenoids, which suppress inflammatory signaling pathways including nuclear factor-kappa B (NF-κB) and cyclooxygenase-2 (COX-2).

Similarly, Eucalyptus globulus has demonstrated potent anti-inflammatory activity owing to its major constituent, 1,8-cineole (eucalyptol). Several studies indicate that eucalyptus essential oil reduces edema, inhibits cytokine production, suppresses oxidative stress, and provides analgesic effects. In addition, its antimicrobial properties help prevent secondary bacterial infections in inflamed or damaged tissues.

The reviewed literature further indicates that topical gel formulations provide effective localized drug delivery by maintaining prolonged contact with the skin, improving penetration of active phytoconstituents, and minimizing systemic adverse effects commonly associated with oral non-steroidal anti-inflammatory drugs (NSAIDs). Most reported formulations exhibited desirable pharmaceutical characteristics, including acceptable pH, suitable viscosity, good spreadability, homogeneity, extrudability, and physical stability during storage.

Overall, the reviewed evidence suggests that polyherbal formulations combining Melia azedarach and Eucalyptus globulus produce greater therapeutic benefits than single-herb formulations because of their synergistic anti-inflammatory, antioxidant, and antimicrobial effects. However, the literature also identifies the need for standardized

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extraction procedures, quality control, toxicity assessment, and large-scale clinical trials before these formulations can be widely adopted in clinical practice.

Summary of Major Findings from Published Studies:

Parameter	Findings Reported in Literature
Anti-inflammatory activity	Significant reduction in inflammatory mediators (TNF-α, IL-1β, IL-6, COX-2)
Antioxidant activity	High free radical scavenging activity due to flavonoids and phenolic compounds
Antimicrobial activity	Effective against common Gram-positive, Gram-negative bacteria and some fungi
Analgesic activity	Reduction in pain associated with inflammation and musculoskeletal disorders
Wound healing	Enhanced fibroblast proliferation, collagen synthesis, and tissue regeneration
Gel characteristics	Good spreadability, homogeneity, viscosity, skin-compatible pH, and stability
Safety	Generally well tolerated in preclinical studies with minimal skin irritation
Future requirement	Standardization, clinical trials, and regulatory validation

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