

Nyctanthes arbor-tristis-Based Topical Emulgel as a Multi-Target Therapeutic Strategy for Gouty Inflammation: Mechanistic Insights and Formulation Perspectives

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ABSTRACT

Gout is a chronic inflammatory disorder characterized by recurrent acute flares resulting from monosodium urate crystal deposition, activation of innate immune pathways, and excessive oxidative stress within affected joints. Although conventional pharmacological therapies such as non-steroidal anti-inflammatory drugs, colchicine, and urate-lowering agents remain the mainstay of treatment, their long-term clinical use is frequently limited by systemic adverse effects, poor patient adherence, and safety concerns, particularly in elderly patients with comorbidities. In this context, plant-based therapeutics combined with advanced topical drug delivery systems offer a promising alternative strategy for localized and safer management of gouty inflammation. *Nyctanthes arbor-tristis* (Harsingar), a medicinal plant widely used in traditional medicine, possesses well-documented anti-inflammatory, antioxidant, analgesic, and immunomodulatory properties attributable to its rich content of iridoid glycosides, flavonoids, and phenolic compounds. This review critically examines the pathophysiology of gout and systematically correlates it with the pharmacological activities of Harsingar, emphasizing its ability to modulate key inflammatory mediators, oxidative stress pathways, and immune cell activation involved in gout progression. Furthermore, the potential of emulgel-based topical delivery systems for improving the stability, skin permeation, and localized bioavailability of Harsingar phytoconstituents is discussed in detail. By integrating ethnopharmacological evidence, mechanistic insights, and formulation strategies, this review highlights Harsingar-based emulgels as a novel, multi-targeted, and patient-friendly therapeutic approach for gout management, while also identifying current research gaps and future directions for clinical translation.

Keywords: Gout, *Nyctanthes arbor-tristis*, Harsingar, Topical emulgel, Anti-inflammatory activity, Antioxidant activity, Plant-based therapeutics.

INTRODUCTION

Gout is a chronic metabolic and inflammatory disorder characterized by recurrent episodes of acute joint pain, swelling, erythema, and functional impairment. The disease primarily results from sustained hyperuricemia, which promotes the crystallization and deposition of monosodium urate crystals in synovial joints and periarticular tissues¹. These crystals act as potent inflammatory stimuli,

triggering innate immune responses that involve activation of the NLRP3 inflammasome and subsequent release of pro-inflammatory mediators such as interleukin-1 β , tumor necrosis factor- α , and interleukin-6. Persistent inflammation not only exacerbates joint damage but also significantly reduces quality of life in affected individuals². The rising global prevalence of gout, driven by dietary habits, sedentary lifestyles, aging populations, and

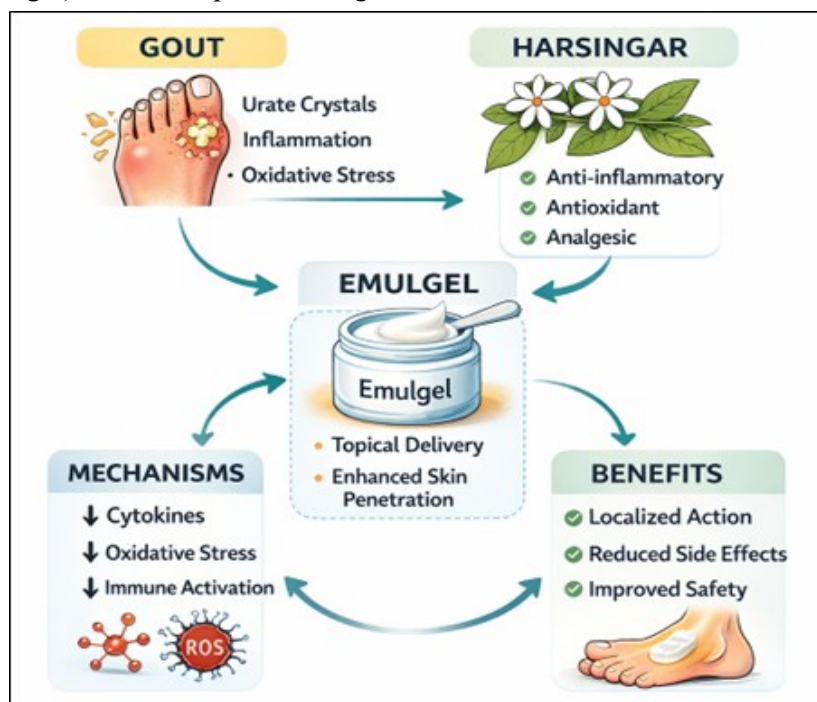
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metabolic comorbidities, highlights the urgent need for effective and safer therapeutic interventions.

Graphical Abstract

Schematic representation of gout pathophysiology and the proposed therapeutic role of a *Nyctanthes arbor-tristis* (Harsingar) based topical emulgel,

highlighting localized multi-target anti-inflammatory action with reduced systemic toxicity.



Conventional pharmacological management of gout relies largely on non-steroidal anti-inflammatory drugs, colchicine, corticosteroids, and urate-lowering agents such as allopurinol and febuxostat³. While these therapies are effective in controlling acute attacks and reducing serum uric acid levels, their long-term use is often limited by adverse effects and clinical contraindications. NSAIDs are associated with gastrointestinal irritation, cardiovascular risks, and renal impairment, whereas colchicine may cause gastrointestinal toxicity and neuromuscular complications, particularly in elderly patients or those with compromised renal function⁴. Urate-lowering therapies require prolonged administration and careful dose monitoring, and in some cases may precipitate acute gout flares during initiation. These limitations frequently result in poor patient adherence and underscore the need for alternative therapeutic strategies that can provide symptomatic relief with reduced systemic burden⁵.

In recent years, there has been growing scientific interest in plant-based therapeutics owing to their structural diversity, multi-targeted mechanisms of action, and relatively favorable safety profiles. Medicinal plants have long been used in traditional systems of medicine for the treatment of inflammatory and arthritic disorders, and modern research has begun to validate many of these traditional claims through pharmacological and mechanistic studies⁶. Alongside this renewed focus on herbal medicines, topical drug delivery systems have gained considerable attention as an effective approach for managing localized inflammatory conditions. Topical formulations offer the advantage of delivering active compounds directly to the site of inflammation, thereby minimizing systemic exposure and reducing the risk of adverse effects. Among various topical systems, emulgels have emerged as a promising platform due to their improved stability, ease of application, enhanced patient acceptability, and ability to incorporate both hydrophilic and lipophilic bioactive compounds⁷.

Nyctanthes arbor-tristis, commonly known as Harsingar or night-flowering jasmine, is a medicinal plant widely recognized in Ayurvedic and traditional medicine for its anti-inflammatory, analgesic, and antioxidant properties. The leaves of the plant are particularly rich in iridoid glycosides, flavonoids, phenolic compounds, and other bioactive constituents that have demonstrated significant pharmacological activity in experimental models of inflammation and arthritis⁸. Traditional use of Harsingar in joint pain, fever, and rheumatic conditions provides a strong ethnopharmacological basis for its selection as a potential therapeutic agent in gouty inflammation. Moreover, the plant's ability to modulate inflammatory mediators and oxidative stress pathways aligns well with the underlying pathophysiology of gout. Despite its therapeutic potential, the clinical application of *Nyctanthes arbor-tristis* remains limited due to challenges associated with the delivery and bioavailability of its phytoconstituents^{9,10}. Conventional oral administration of herbal extracts often results in poor absorption, rapid metabolism, and inconsistent therapeutic outcomes. In this context, incorporating Harsingar extracts into advanced topical delivery systems such as emulgels represents a rational and innovative approach to enhance local drug concentration, improve skin permeation, and achieve sustained anti-inflammatory effects at the affected site¹¹.

Table 1 provides a comparative perspective between conventional systemic gout therapies and the proposed Harsingar (*Nyctanthes arbor-tristis*)-based topical emulgel, underscoring key differences in therapeutic approach, safety profile, and mechanism of action. Conventional agents such as NSAIDs, colchicine, and urate-lowering drugs primarily exert systemic effects and are associated with gastrointestinal, renal, and cardiovascular adverse outcomes, which often limit their long-term use and patient adherence¹². In contrast, the topical emulgel strategy offers localized delivery of bioactive phytoconstituents directly to the inflamed joint, thereby minimizing systemic exposure while maintaining effective anti-inflammatory and analgesic action. Notably, unlike standard therapies that act on single molecular targets, the Harsingar emulgel demonstrates a multi-target pharmacological profile, integrating anti-inflammatory, antioxidant, analgesic, and immunomodulatory effects that align closely with the multifactorial pathophysiology of gout¹³. The absence of flare induction during treatment initiation and the reduced requirement for laboratory monitoring further support its suitability for chronic and elderly patients. Collectively, this comparison highlights the potential of Harsingar-based emulgels as a safer and patient-friendly adjunct or alternative to conventional gout management strategies¹⁴.

Table 1: Comparative overview of conventional systemic gout therapies and the proposed Harsingar (*Nyctanthes arbor-tristis*)-based topical emulgel, highlighting differences in route of administration, therapeutic targets, safety profile, and multi-target anti-inflammatory potential.

<u>S. No</u>	Parameter	NSAIDs/Colchicine	Urate-Lowering Drugs	Harsingar Emulgel	References
1	Route of administration	Oral	Oral	Topical	15
2	Primary therapeutic goal	Acute inflammation control	Serum uric acid reduction	Local inflammation and pain control	16
3	Main biological target	COX enzymes/microtubules	Xanthine oxidase	Inflammatory mediators + ROS	17
4	Site of action	Systemic	Systemic	Localized (affected joint)	18
5	Effect on hyperuricemia	No	Yes	Indirect/supportive	19



6	Anti-inflammatory action	Strong	Indirect	Strong (multi-pathway)	20
7	Antioxidant activity	Minimal	None	High	21
8	Analgesic potential	High	Low	Moderate-High	22
9	Immunomodulatory effect	Non-selective	None	Balanced immune modulation	23
10	Risk of GI toxicity	High	Moderate	Very low	24
11	Renal safety concerns	Significant	Significant	Minimal	25
12	Cardiovascular risk	Present	Reported	Negligible	26
13	Risk of acute flare on initiation	No	Yes	No	27
14	Suitability for elderly patients	Limited	Cautious use	Highly suitable	28
15	Drug-drug interaction risk	High	Moderate	Low	29
16	Long-term use feasibility	Poor	Moderate	Good	30
17	Patient compliance	Low	Moderate	High	31
18	Need for laboratory monitoring	Frequent	Essential	Not required	32
19	Overall safety-efficacy balance	Moderate	Moderate	Favorable	33

2. Pathophysiology of Gouty Inflammation

Gouty inflammation is a complex pathological process primarily driven by disturbances in purine metabolism that result in sustained elevation of serum uric acid levels. Uric acid is the final metabolic product of purine degradation in humans due to the absence of the enzyme uricase, which converts uric acid into the more soluble allantoin in other species. When the concentration of uric acid exceeds its physiological solubility limit, particularly in peripheral joints where temperature and blood flow are relatively lower, monosodium urate crystals begin to form and deposit within synovial fluid and surrounding tissues. These needle-shaped crystals are recognized as danger-associated molecular patterns by resident immune cells, initiating a robust inflammatory response that underlies the clinical manifestations of gout³⁴.

The deposition of monosodium urate crystals serves as a potent trigger for innate immune activation. Phagocytosis of these crystals by macrophages leads to destabilization of lysosomal membranes and

subsequent activation of the NLRP3 inflammasome, a multiprotein complex that plays a central role in gouty inflammation. Activation of the NLRP3 inflammasome results in the cleavage of pro-caspase-1 into its active form, which in turn promotes the maturation and release of interleukin-1 β , a key cytokine responsible for amplifying the inflammatory cascade. Interleukin-1 β stimulates the recruitment of neutrophils to the affected joint and enhances the production of additional pro-inflammatory mediators, including tumor necrosis factor- α and interleukin-6, thereby perpetuating tissue inflammation and pain³⁵.

Neutrophil infiltration represents a hallmark feature of acute gout attacks. These cells respond to chemotactic signals generated in the inflamed joint and contribute to tissue damage through the release of proteolytic enzymes, inflammatory cytokines, and reactive oxygen species. The excessive generation of reactive oxygen species further exacerbates joint inflammation by inducing oxidative stress, which disrupts cellular redox homeostasis and promotes lipid peroxidation, protein oxidation, and DNA damage. Oxidative stress not only intensifies



inflammatory signaling pathways but also enhances the persistence of monosodium urate crystals by altering the local microenvironment within the joint².

Immune cell activation in gout extends beyond neutrophils and macrophages, involving dendritic cells, mast cells, and endothelial cells that collectively contribute to vascular permeability, edema, and sustained inflammation. The interplay between immune cells and oxidative stress creates a self-amplifying loop in which inflammatory mediators increase reactive oxygen species production, while oxidative stress further activates pro-inflammatory transcription factors such as nuclear factor- κ B. This interconnected network of metabolic imbalance, crystal deposition, immune activation, and oxidative damage explains the recurrent and often severe nature of gouty inflammation³⁶.

Understanding the localized nature of this inflammatory process has important therapeutic implications. Since gout flares typically affect superficial joints and periarticular tissues, targeted delivery of anti-inflammatory agents directly to the site of inflammation offers a rational treatment strategy. Topical anti-inflammatory therapy can

potentially suppress local cytokine production, reduce oxidative stress, and inhibit immune cell activation without exposing patients to the systemic adverse effects commonly associated with oral pharmacological agents. By maintaining higher drug concentrations at the inflamed site and limiting systemic absorption, topical formulations may provide effective symptomatic relief while improving patient safety and compliance. Advanced topical delivery systems such as emulgels present a promising approach for managing gouty inflammation³⁷. Emulgels can enhance the penetration of anti-inflammatory compounds through the skin barrier and allow sustained release of active agents at the target site. When combined with plant-derived bioactives possessing antioxidant and immunomodulatory properties, topical emulgel systems may effectively interrupt the pathological cascade of gout by attenuating oxidative stress, inhibiting pro-inflammatory cytokine release, and modulating immune responses. This localized therapeutic strategy aligns closely with the underlying pathophysiology of gout and represents a scientifically justified alternative to conventional systemic treatment modalities³⁸.

Figure 1: Illustrates the pathophysiology of gouty inflammation beginning with hyperuricemia caused by dietary purines, leading to monosodium urate (MSU) crystal deposition in joints. This activates immune cells, triggers cytokine release, and induces oxidative stress, resulting in inflammation and joint damage. Plant-based bioactive emulgel therapy may reduce cytokines, oxidative stress, and inflammation



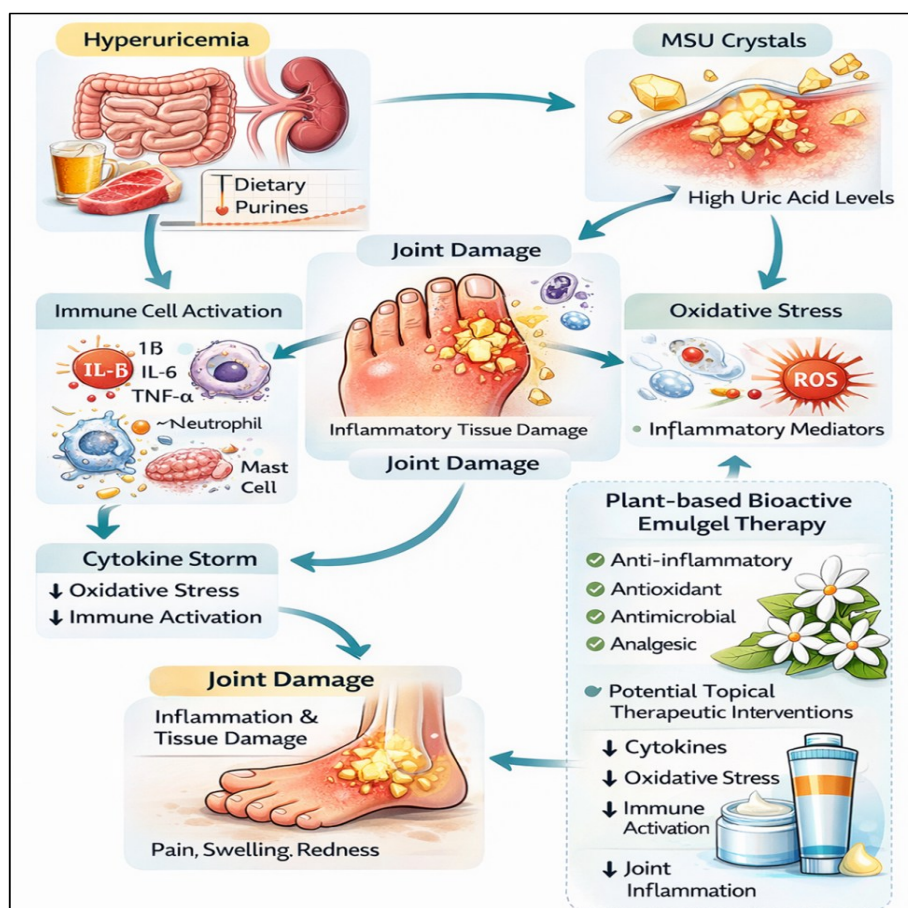


Figure 1: Pathophysiology of Gouty Inflammation: From Hyperuricemia to Joint Damage and Potential Topical Therapeutic Interventions. The diagram illustrates uric acid accumulation, MSU crystal deposition, immune cell activation, cytokine storm, oxidative stress, and the rationale for plant-based bioactive emulgel therapy

3. Limitations of Conventional Gout Management

Conventional management of gout primarily relies on systemic pharmacological agents aimed at controlling acute inflammatory episodes and reducing serum uric acid levels. Although these drugs are clinically effective, their widespread and long-term use is often constrained by a range of systemic adverse effects. Non-steroidal anti-inflammatory drugs remain the first-line therapy for acute gout flares; however, their mechanism of action involves inhibition of cyclooxygenase enzymes throughout the body, which frequently results in gastrointestinal irritation, ulceration, and bleeding. Prolonged NSAID use is also associated with renal hemodynamic alterations and an increased risk of cardiovascular events, particularly in elderly patients and those with pre-existing comorbidities³⁹.

Colchicine, another commonly prescribed anti-gout medication, exerts its anti-inflammatory effect by disrupting microtubule polymerization and inhibiting neutrophil migration. Despite its efficacy, colchicine possesses a narrow therapeutic window and is frequently associated with dose-dependent gastrointestinal toxicity, including nausea, vomiting, and diarrhea. In patients with impaired renal or hepatic function, colchicine accumulation may lead to severe neuromuscular and hematological complications. These safety concerns often necessitate dose reduction or discontinuation, limiting its suitability for long-term management⁴⁰.

Urate-lowering therapies such as allopurinol and febuxostat are central to the prevention of recurrent gout attacks; however, their clinical utility is challenged by several factors. Initiation of urate-lowering therapy can paradoxically trigger acute gout flares, which discourages patient adherence during the

early phase of treatment. Moreover, hypersensitivity reactions, hepatotoxicity, renal dysfunction, and potential cardiovascular risks have been reported with prolonged use of these agents. The requirement for continuous monitoring of serum uric acid levels and dose adjustments further complicates therapy, particularly in patients with multiple comorbid conditions⁴¹.

Poor patient compliance represents a major barrier to effective gout management. The chronic nature of the disease demands long-term or lifelong pharmacotherapy, which many patients find difficult to maintain due to side effects, complex dosing regimens, and delayed therapeutic benefits. Non-adherence often leads to uncontrolled hyperuricemia, frequent disease flares, and progressive joint damage. Additionally, lifestyle modifications recommended alongside pharmacological treatment, such as dietary restrictions and alcohol avoidance, are not consistently followed, further reducing overall treatment effectiveness⁴².

The systemic exposure associated with oral anti-gout medications poses significant risks to vital organs, especially the gastrointestinal tract, kidneys, and cardiovascular system. Patients with gout frequently present with comorbidities such as hypertension, diabetes, chronic kidney disease, and cardiovascular disorders, which increase their vulnerability to drug-induced toxicity. In such populations, the use of systemic anti-inflammatory and urate-lowering agents may be contraindicated or require cautious administration, thereby limiting therapeutic options. These limitations highlight a critical need for alternative treatment strategies that can provide effective symptom control while minimizing systemic adverse effects. Localized therapeutic approaches that target inflamed joints directly offer a promising solution by reducing systemic drug exposure and associated risks. Topical anti-inflammatory formulations, particularly those utilizing advanced delivery systems, have the potential to achieve high drug concentrations at the site of inflammation, improve safety profiles, and enhance patient adherence. Such approaches are especially appealing for chronic conditions like gout, where long-term management and patient comfort are essential for successful disease control⁴³.

4. *Nyctanthes arbor-tristis* (Harsingar): Botanical and Ethnomedicinal Profile

Nyctanthes arbor-tristis, commonly known as Harsingar or night-flowering jasmine, is a small to medium-sized deciduous tree belonging to the family Oleaceae. The plant is characterized by rough, quadrangular branches, opposite ovate leaves with a rough surface, and highly fragrant white flowers with a distinctive orange tubular center that bloom at night and shed by morning. These morphological features make the plant easily recognizable and widely cultivated in home gardens and temple premises⁴⁴. *Nyctanthes arbor-tristis* is native to the Indian subcontinent and Southeast Asia and is extensively distributed across India, Nepal, Bangladesh, Sri Lanka, Thailand, and parts of Indonesia. It thrives in tropical and subtropical climates and adapts well to a variety of soil conditions, contributing to its widespread availability and traditional medicinal use⁴⁵. The ethnomedicinal significance of *Nyctanthes arbor-tristis* is deeply rooted in traditional healthcare systems, where different parts of the plant, particularly the leaves, flowers, seeds, and bark, have been used for centuries to manage a variety of ailments. The leaves are most commonly employed for their anti-inflammatory, antipyretic, and analgesic properties and are traditionally administered in the form of decoctions, juices, or pastes for the treatment of joint pain, arthritis, sciatica, and rheumatic disorders. Inflammatory conditions associated with fever and chronic pain have also been managed using leaf extracts, reflecting the plant's broad therapeutic relevance. The flowers have been used as mild sedatives and for managing digestive disorders, while seeds and bark have found applications in the treatment of skin diseases and parasitic infections⁴⁶.

In Ayurvedic medicine, Harsingar holds a prominent position and is described in classical texts for its ability to balance doshas associated with inflammatory and musculoskeletal disorders. The plant is traditionally recommended for conditions involving stiffness, swelling, and pain, which closely resemble the clinical manifestations of gout and arthritis. Folk medicine practices across rural India and neighboring regions further support its use in chronic inflammatory diseases, where it is often preferred due to its perceived safety and natural



origin. The continued reliance on *Nyctanthes arbor-tristis* in traditional healing practices underscores its therapeutic credibility and provides a strong ethnopharmacological foundation for modern scientific investigation⁴⁷.

From a safety perspective, *Nyctanthes arbor-tristis* is generally considered to possess a favorable toxicity profile when used in traditional doses. Preclinical studies have reported minimal acute and sub-acute toxicity of leaf extracts, with no significant alterations in vital organ function or hematological parameters at therapeutic concentrations. However, excessive or prolonged consumption of concentrated extracts may lead to mild gastrointestinal discomfort, emphasizing the importance of dose standardization. The relative safety of the plant, combined with its long history of human use, enhances its suitability for incorporation into topical formulations aimed at chronic inflammatory conditions⁴⁸. Nonetheless, comprehensive toxicological evaluations and clinical studies remain essential to ensure consistent safety, particularly when developing standardized pharmaceutical preparations.

The botanical characteristics, wide geographical distribution, extensive traditional use, and acceptable safety profile of *Nyctanthes arbor-tristis* support its selection as a promising plant candidate for the management of inflammatory disorders. Its ethnomedicinal relevance, especially in arthritis-like conditions, provides a compelling rationale for exploring its therapeutic potential through modern drug delivery approaches such as emulgel systems, which may further enhance efficacy while maintaining safety⁴⁹.

5. Phytochemical Composition of Harsingar

The therapeutic potential of *Nyctanthes arbor-tristis* is largely attributed to its rich and diverse phytochemical profile, which includes a wide range of bioactive secondary metabolites. Among these, iridoid glycosides represent the most characteristic and pharmacologically significant class of compounds identified in the plant. Nyctanthoside and arbortristoside are the principal iridoid glycosides reported in the leaves and are considered key contributors to the plant's anti-inflammatory and immunomodulatory activities. These compounds are

known to interfere with inflammatory signaling pathways by modulating cytokine production and suppressing enzymatic mediators involved in inflammation, thereby supporting the traditional use of Harsingar in arthritic and inflammatory conditions.

In addition to iridoid glycosides, *Nyctanthes arbor-tristis* contains a variety of flavonoids and phenolic compounds that contribute substantially to its antioxidant potential. Flavonoids such as quercetin derivatives and related polyphenols are recognized for their ability to scavenge reactive oxygen species and inhibit lipid peroxidation. The presence of these compounds is particularly relevant in gouty inflammation, where oxidative stress plays a critical role in amplifying inflammatory responses and tissue damage. By reducing oxidative burden, these phytoconstituents may indirectly attenuate inflammatory cascades and protect joint tissues from further injury⁵⁰. Sterols and essential oils identified in different parts of the plant further enhance its pharmacological profile. Phytosterols are known to exhibit anti-inflammatory and membrane-stabilizing effects, while volatile constituents present in essential oils may contribute to analgesic and antimicrobial activities. Although present in relatively smaller quantities compared to iridoids and flavonoids, these compounds may act synergistically to enhance the overall therapeutic efficacy of the plant extract. Such synergism among multiple phytochemicals is a hallmark of herbal medicines and offers a multi-targeted approach to disease management.

The anti-inflammatory and antioxidant effects of *Nyctanthes arbor-tristis* are not attributed to a single compound but rather to the combined action of its diverse bioactive constituents. Iridoid glycosides modulate inflammatory mediators, flavonoids and phenolics counteract oxidative stress, and sterols contribute to membrane stabilization and immune regulation. This multi-component pharmacological activity aligns well with the complex pathophysiology of inflammatory disorders such as gout, where multiple biochemical pathways are involved⁵¹.

The phytochemical composition of Harsingar is influenced by several factors, including the plant part used, geographical origin, stage of growth, and extraction method. Leaves are generally reported to



contain higher concentrations of iridoid glycosides and flavonoids, making them the most commonly utilized part for medicinal purposes. Flowers and seeds exhibit a distinct phytochemical profile, with variations in volatile and phenolic constituents. Extraction techniques such as aqueous, ethanolic, or hydroalcoholic extraction significantly affect the yield and composition of bioactive compounds, with polar solvents typically enhancing the extraction of glycosides and phenolics. Such variability underscores the importance of standardization in the development of pharmaceutical formulations to ensure reproducible therapeutic outcomes⁵².

6. Pharmacological Activities Relevant to Gout

The pharmacological relevance of *Nyctanthes arbor-tristis* in the management of gouty inflammation is supported by its broad spectrum of anti-inflammatory, antioxidant, analgesic, and immunomodulatory activities. These therapeutic effects are particularly important in gout, where inflammation is driven by complex interactions between monosodium urate crystals, immune cell activation, and oxidative stress. Experimental studies have demonstrated that extracts of *Nyctanthes arbor-tristis*, especially those derived from the leaves, exert significant anti-inflammatory effects by modulating key enzymatic and cytokine-mediated pathways involved in inflammatory responses⁵³.

One of the primary mechanisms underlying the anti-inflammatory activity of *Nyctanthes arbor-tristis* involves the inhibition of cyclooxygenase enzymes, which are responsible for the synthesis of pro-inflammatory prostaglandins. Suppression of prostaglandin production leads to a reduction in inflammation-associated pain, swelling, and erythema. In addition to cyclooxygenase inhibition, the plant has been shown to modulate the release of pro-inflammatory cytokines such as interleukin-1 β , tumor necrosis factor- α , and interleukin-6. These cytokines play a central role in the amplification of gouty inflammation by promoting immune cell recruitment and sustaining inflammatory signaling cascades. By downregulating cytokine production, *Nyctanthes arbor-tristis* may effectively interrupt the progression of acute inflammatory episodes associated with gout⁵⁴.

Oxidative stress is a critical contributor to the pathogenesis of gout, as excessive generation of reactive oxygen species enhances inflammatory signaling and tissue damage within affected joints. *Nyctanthes arbor-tristis* exhibits pronounced antioxidant activity, which has been attributed to its rich content of flavonoids, phenolic compounds, and iridoid glycosides. These phytoconstituents act as free radical scavengers, neutralizing reactive oxygen species and preventing oxidative damage to cellular membranes, proteins, and nucleic acids⁵⁵. By restoring redox balance, the antioxidant properties of the plant may reduce the severity and duration of gout flares while protecting joint tissues from progressive degeneration.

In addition to its anti-inflammatory and antioxidant actions, *Nyctanthes arbor-tristis* demonstrates notable analgesic effects that are relevant to the management of gout-associated pain. Preclinical studies have reported significant reductions in pain perception following administration of plant extracts in experimental pain models. These effects are likely mediated through both peripheral and central mechanisms, including inhibition of inflammatory mediators and modulation of nociceptive signaling pathways. The analgesic activity of the plant enhances its therapeutic value by addressing one of the most debilitating symptoms of gout⁵⁶.

The immunomodulatory properties of *Nyctanthes arbor-tristis* further contribute to its potential utility in gout management. The plant has been reported to regulate immune cell activity by influencing macrophage and neutrophil function, thereby limiting excessive inflammatory responses. By modulating immune cell activation rather than broadly suppressing immunity, *Nyctanthes arbor-tristis* may offer a balanced approach to controlling inflammation with a lower risk of immunosuppression-related complications⁵⁷. This feature is particularly advantageous in chronic inflammatory conditions where long-term therapy is required.

Preclinical evidence supporting the efficacy of *Nyctanthes arbor-tristis* has been obtained from various in vivo and in vitro models of inflammation and arthritis. Animal studies using experimentally induced arthritis and inflammatory pain models have



demonstrated significant reductions in joint swelling, inflammatory markers, and oxidative stress following treatment with plant extracts. These findings provide a scientific basis for the traditional use of Harsingar in arthritic conditions and suggest its potential applicability in gout, which shares overlapping inflammatory mechanisms with other forms of arthritis⁵⁸.

The pharmacological activities of *Nyctanthes arbor-tristis* align closely with the multifactorial pathophysiology of gouty inflammation. Its ability to simultaneously inhibit inflammatory mediators, scavenge reactive oxygen species, alleviate pain, and modulate immune responses positions it as a promising natural therapeutic agent. When incorporated into advanced topical delivery systems such as emulgels, these pharmacological properties may be further enhanced, offering a targeted and safer alternative for the management of gout⁵⁹.

7. Emulgel Drug Delivery Systems

Emulgel drug delivery systems represent a hybrid topical formulation that integrates the properties of emulsions and gels to overcome the limitations associated with conventional topical dosage forms. Conceptually, an emulgel consists of an emulsion, either oil-in-water or water-in-oil, that is incorporated into a gel base, resulting in a stable, semisolid system with enhanced drug-loading capacity and improved patient acceptability. Based on the nature of the internal phase, emulgels are generally classified as oil-in-water or water-in-oil systems, with oil-in-water emulgels being more commonly used for topical application due to their non-greasy nature, ease of removal, and better skin compatibility⁶⁰. This dual-phase structure allows emulgels to accommodate a wide range of active pharmaceutical ingredients, including both hydrophilic and lipophilic compounds, making them particularly suitable for complex herbal extracts.

Compared to conventional gels, creams, and ointments, emulgels offer several distinct advantages that enhance their therapeutic performance. Traditional gels often exhibit limited drug-loading capacity for hydrophobic compounds, while creams and ointments may suffer from poor stability, greasy texture, and low patient compliance. Emulgels

address these challenges by combining the solubilization capacity of emulsions with the rheological benefits of gels. The presence of a gel matrix improves viscosity, spreadability, and residence time on the skin, while the emulsified phase facilitates efficient incorporation and uniform distribution of lipophilic drugs. These attributes result in improved physical stability, controlled drug release, and enhanced patient comfort during application⁶¹.

The formulation of emulgels involves the careful selection of multiple components, each playing a critical role in determining the final product performance. The oil phase serves as a carrier for lipophilic drugs and influences skin penetration, with commonly used oils including mineral oil, isopropyl myristate, and various natural oils. Surfactants and co-surfactants are employed to stabilize the emulsion by reducing interfacial tension between the oil and aqueous phases, thereby ensuring homogeneity and long-term stability⁶². Non-ionic surfactants are often preferred due to their lower irritation potential and better compatibility with the skin. Gelling agents such as Carbopol, hydroxypropyl methylcellulose, and other synthetic or natural polymers are incorporated to impart the desired viscosity and structural integrity to the formulation. The choice and concentration of these polymers significantly influence spreadability, drug release behavior, and sensory attributes.

Skin penetration and drug release from emulgel systems are governed by multiple interconnected mechanisms⁶³. Upon topical application, the gel matrix facilitates prolonged contact with the skin surface, allowing sufficient time for drug diffusion. The emulsified oil droplets act as reservoirs that gradually release the active compound, enabling sustained drug delivery. Additionally, certain oils and surfactants function as penetration enhancers by interacting with the stratum corneum lipids, thereby increasing skin permeability. Drug release from emulgels typically occurs through diffusion-controlled mechanisms, where the active ingredient migrates from the internal phase through the gel network and into the skin layers. The rate of release can be modulated by adjusting formulation parameters such as polymer concentration, droplet size, and oil-to-water ratio⁶⁴.



8. Formulation Strategies for Harsingar-Based Emulgels

The formulation of emulgels incorporating *Nyctanthes arbor-tristis* requires a systematic and rational approach to ensure consistent therapeutic performance, stability, and patient acceptability. The selection of the plant extract represents a critical initial step, as the pharmacological efficacy of the formulation is directly influenced by the quality and composition of the extract. Leaves of *Nyctanthes arbor-tristis* are generally preferred due to their higher content of iridoid glycosides, flavonoids, and phenolic compounds⁶⁵. Extraction methods must be carefully chosen to preserve bioactive constituents, with hydroalcoholic or ethanolic extraction commonly employed to achieve optimal yield. Standardization of the extract using marker compounds such as nyctanthoside or arbortristoside is essential to ensure batch-to-batch consistency and reproducible therapeutic outcomes. Analytical techniques including high-performance liquid chromatography and spectrophotometric assays are frequently used for this purpose.

The choice of oil phase plays a pivotal role in solubilizing lipophilic phytoconstituents and enhancing skin permeation. Oils such as isopropyl myristate, liquid paraffin, and selected natural oils are often utilized due to their compatibility with topical formulations and penetration-enhancing properties⁶⁵. Emulsifying agents are selected to stabilize the oil and aqueous phases and to maintain the integrity of the emulgel system over time. Non-ionic surfactants are commonly preferred because of their lower irritation potential and improved skin tolerance. The appropriate selection and concentration of surfactants and co-surfactants contribute significantly to emulsion stability, droplet size distribution, and drug release behavior⁶⁶.

Gelling polymers are incorporated to impart suitable viscosity, enhance spreadability, and ensure prolonged residence of the formulation on the skin. Synthetic polymers such as Carbopol are widely used due to their excellent gelling efficiency and ability to produce clear, stable gels at low concentrations. Hydroxypropyl methylcellulose offers an alternative with good film-forming properties and compatibility

with a wide range of active ingredients. Natural polymers, including xanthan gum and guar gum, are increasingly explored due to their biodegradability and favorable safety profiles⁶⁷. The selection of an appropriate polymer and its concentration is crucial for achieving the desired rheological properties and controlled drug release.

Optimization of formulation parameters is essential to achieve an emulgel with acceptable physicochemical and sensory characteristics. The pH of the formulation should be adjusted to match the physiological pH of the skin to minimize irritation and enhance patient comfort. Viscosity influences both the ease of application and drug release kinetics, requiring careful balancing to ensure adequate spreadability without compromising stability. Spreadability is an important quality attribute that affects patient compliance and uniform drug distribution across the skin surface⁶⁸. These parameters are typically optimized through systematic experimental design and rheological evaluation.

Stability considerations are of paramount importance in the development of Harsingar-based emulgels, as herbal extracts are susceptible to degradation under unfavorable conditions. Factors such as temperature, light, and humidity can influence the physical and chemical stability of the formulation. Stability studies are conducted to assess changes in appearance, pH, viscosity, phase separation, and drug content over time. The incorporation of suitable antioxidants and preservatives may be necessary to enhance shelf-life and prevent microbial growth. Ensuring long-term stability not only supports therapeutic efficacy but also facilitates regulatory approval and commercialization⁶⁹.

9. Evaluation Parameters of Harsingar Emulgels

Comprehensive evaluation of Harsingar-based emulgels is essential to establish their quality, performance, safety, and therapeutic relevance for topical application in gouty inflammation. Physicochemical characterization represents the primary step in formulation assessment and includes the evaluation of appearance, homogeneity, pH, viscosity, spreadability, and drug content uniformity. Visual inspection ensures the absence of phase separation, grittiness, or color changes, while pH



measurement confirms compatibility with the skin environment. Rheological studies provide insight into viscosity and flow behavior, which influence both patient acceptability and drug release characteristics. Uniform distribution of the plant extract within the formulation is crucial to ensure consistent therapeutic effect across applications⁶⁷.

In vitro drug release studies are conducted to evaluate the release profile of bioactive constituents from the emulgel matrix and to predict their availability at the site of action. These studies are commonly performed using diffusion cells with suitable membranes and release media that simulate physiological conditions. The cumulative release data obtained are analyzed using various kinetic models such as zero-order, first-order, Higuchi, and Korsmeyer-Peppas equations to elucidate the underlying drug release mechanism. Understanding release kinetics is particularly important for herbal formulations, as it helps optimize polymer concentration and formulation composition to achieve sustained and controlled delivery of phytoconstituents⁶⁹.

Ex vivo skin permeation studies provide critical information on the ability of Harsingar emulgels to deliver active compounds across the skin barrier. These studies are typically performed using excised animal or human skin mounted on diffusion cells to assess the extent and rate of permeation. Parameters such as permeation flux, permeability coefficient, and drug retention within skin layers are evaluated to determine the formulation's effectiveness in delivering phytoconstituents to inflamed tissues. Enhanced permeation and localized drug retention are desirable outcomes, as they support targeted therapy while minimizing systemic exposure.

Biological evaluation of Harsingar-based emulgels includes assessment of anti-inflammatory and antioxidant activities, which are central to their therapeutic role in gout management. Anti-inflammatory efficacy may be evaluated using suitable in vivo or in vitro models that measure reductions in edema, inflammatory markers, or cytokine levels. Antioxidant activity is assessed through established assays that determine the formulation's ability to neutralize reactive oxygen species and reduce oxidative stress⁶⁸. These

evaluations help correlate pharmacological activity with phytochemical composition and formulation design.

Safety assessment is a critical component of emulgel evaluation, particularly for formulations intended for repeated or long-term use. Skin irritation and sensitization studies are conducted to ensure that the formulation does not induce erythema, edema, or allergic reactions upon topical application. These studies provide essential data on dermal tolerance and help establish the formulation's suitability for clinical use. The favorable safety profile of *Nyctanthes arbor-tristis*, combined with careful formulation design, supports the development of emulgels that are both effective and well tolerated⁷⁰.

10. Therapeutic Potential of Harsingar Emulgels in Gouty Inflammation

Harsingar-based emulgels present significant therapeutic potential in the management of gouty inflammation by offering a targeted and localized drug delivery approach that aligns closely with the pathophysiological characteristics of the disease. Gout flares typically involve superficial joints and periarticular tissues, making them highly amenable to topical intervention. By delivering bioactive phytoconstituents of *Nyctanthes arbor-tristis* directly to the inflamed site, emulgel formulations can achieve higher local drug concentrations while limiting systemic distribution⁷¹. This localized action allows effective suppression of inflammatory mediators, oxidative stress, and pain at the affected joint, thereby providing rapid symptomatic relief.

One of the major advantages of Harsingar emulgels lies in their ability to reduce systemic adverse effects commonly associated with conventional oral anti-gout medications. Systemic therapies such as NSAIDs, colchicine, and urate-lowering agents expose multiple organs to pharmacological action, increasing the risk of gastrointestinal irritation, renal dysfunction, and cardiovascular complications. In contrast, topical emulgel delivery minimizes systemic absorption of active compounds, thereby lowering the likelihood of off-target toxicity. This safety advantage is particularly relevant for gout patients who often present with comorbid conditions that restrict the use of systemic drugs⁷².



Improved patient compliance is another critical benefit associated with Harsingar-based emulgel therapy. Topical formulations are generally easy to apply, non-invasive, and associated with fewer adverse effects, making them more acceptable for long-term use. The non-greasy texture, good spreadability, and pleasant sensory attributes of emulgels further enhance patient adherence to treatment regimens. Consistent use of such formulations may help reduce the frequency and severity of gout flares, contributing to better disease control and improved quality of life⁷³.

When compared with conventional topical dosage forms such as creams, ointments, and gels, emulgels offer superior therapeutic performance. Traditional creams and ointments often suffer from poor stability, limited drug penetration, and unfavorable sensory characteristics, which can reduce patient acceptance. Simple gels, while cosmetically acceptable, may be inadequate for delivering lipophilic phytoconstituents present in herbal extracts. Emulgels overcome these limitations by combining the solubilization capacity of emulsions with the structural advantages of gels, enabling efficient incorporation and sustained release of bioactive compounds. The presence of penetration-enhancing components in emulgels further facilitates drug transport across the skin barrier, enhancing therapeutic efficacy⁷⁴.

11. Current Research Gaps and Challenges

Despite promising preclinical evidence supporting the anti-inflammatory and antioxidant properties of Harsingar-based formulations, several critical research gaps and challenges continue to limit their translational and clinical relevance. One of the most significant limitations is the lack of well-designed clinical studies evaluating the safety, efficacy, and long-term benefits of Harsingar emulgels in patients with gouty inflammation. Most available data are derived from *in vitro* assays or animal models that do not fully replicate the complex pathophysiology of human gout, particularly the role of monosodium urate crystal deposition and recurrent inflammatory flares⁷⁵. The absence of randomized controlled clinical trials restricts the ability to establish therapeutic dosing, treatment duration, and

comparative effectiveness against standard anti-gout therapies.

Standardization and reproducibility represent another major challenge in the development of Harsingar-based emulgels. Variability in plant source, geographical origin, harvesting season, extraction methods, and phytochemical composition can lead to significant batch-to-batch differences in biological activity. Such inconsistencies complicate formulation optimization and make it difficult to reproduce experimental outcomes across different research settings. Moreover, the lack of validated analytical markers for quality control and standardization of Harsingar extracts further hampers regulatory acceptance and large-scale manufacturing⁷⁶.

Limited mechanistic understanding of the action of Harsingar emulgels in gout-specific models also remains a critical gap. While anti-inflammatory effects have been demonstrated through general inflammatory markers, detailed investigations into gout-relevant pathways such as NLRP3 inflammasome activation, interleukin-1 β signaling, oxidative stress induced by urate crystals, and neutrophil recruitment are still insufficient. The absence of mechanistic studies using monosodium urate crystal-induced inflammation models reduces confidence in the direct applicability of these formulations for gout management and highlights the need for disease-specific experimental validation.

Stability and shelf-life concerns further pose practical challenges in the development of Harsingar emulgels. Herbal formulations are inherently prone to physicochemical instability due to the complex nature of phytoconstituents, which may undergo oxidation, hydrolysis, or microbial degradation over time⁷⁷. Emulgels, in particular, may face issues such as phase separation, changes in viscosity, pH variation, and loss of drug content during storage. Inadequate stability data under accelerated and long-term storage conditions limit the feasibility of commercial development and restrict regulatory approval. Addressing these challenges requires systematic stability studies, optimization of formulation components, and incorporation of suitable preservatives and stabilizers⁷⁸.



12. Future Perspectives

Future advancements in Harsingar-based emulgel systems are expected to be driven by the integration of nanotechnology, which holds considerable promise for enhancing therapeutic efficacy and skin penetration. Incorporation of nanosized carriers such as nanoemulsions, solid lipid nanoparticles, nanostructured lipid carriers, or polymeric nanoparticles within emulgel matrices can significantly improve the solubility, stability, and bioavailability of Harsingar phytoconstituents⁷⁹. These nano-integrated emulgels may facilitate deeper and more controlled penetration through the stratum corneum, allowing efficient delivery of bioactive compounds to inflamed periarticular tissues. Such systems also offer sustained drug release profiles, reducing application frequency and improving patient adherence, which is particularly beneficial in chronic and recurrent gout conditions.

Another promising future direction involves the development of combination therapeutic strategies that integrate Harsingar emulgels with conventional urate-lowering agents. While Harsingar primarily addresses inflammation, oxidative stress, and pain, urate-lowering drugs target the underlying hyperuricemia responsible for gout progression⁸⁰. A dual-approach regimen combining topical Harsingar-based emulgels with systemic or topical urate-lowering therapies could provide comprehensive disease management by simultaneously controlling inflammation and preventing crystal deposition. Such combination therapy has the potential to reduce required doses of synthetic drugs, thereby minimizing systemic toxicity and adverse effects commonly associated with long-term gout treatment⁸¹.

The evolution of smart and stimuli-responsive topical delivery systems represents an emerging and innovative perspective in gout management. Advanced emulgels designed to respond to specific physiological stimuli such as pH changes, temperature elevation, enzymatic activity, or inflammatory mediators could enable site-specific and on-demand drug release. In gouty inflammation, localized changes in skin temperature, oxidative stress levels, and inflammatory biomarkers could be exploited to trigger enhanced release of Harsingar

phytoconstituents precisely at the affected joint. This targeted approach may improve therapeutic precision, reduce unnecessary drug exposure to healthy tissues, and enhance overall treatment outcomes⁸².

Personalized herbal therapeutics also represent a future paradigm shift in the management of gout using Harsingar-based formulations. Individual variability in disease severity, inflammatory response, skin permeability, and metabolic profile suggests that a one-size-fits-all approach may not be optimal. Personalized emulgel formulations tailored to patient-specific factors such as flare frequency, joint involvement, skin type, and sensitivity could improve efficacy and tolerability. Advances in phytochemical profiling, formulation customization, and patient stratification may support the development of individualized herbal topical therapies, aligning traditional plant-based medicine with modern precision healthcare concepts⁸³.

13. CONCLUSION

The present review demonstrates that Harsingar (*Nyctanthes arbor-tristis*)-based emulgels possess significant anti-inflammatory, antioxidant, and analgesic properties, making them a promising topical therapeutic option for gout management. Key findings include the plant's rich phytochemical profile comprising iridoid glycosides, flavonoids, and phenolic compounds that effectively modulate inflammatory mediators, reduce oxidative stress, and alleviate pain through multi-targeted mechanisms. The incorporation of Harsingar extract into emulgel systems offers several advantages over conventional topical formulations, including enhanced skin permeation, sustained drug release, improved stability, and superior patient acceptability. The emulgel platform addresses critical limitations of systemic gout therapies by enabling localized drug delivery, minimizing systemic adverse effects, and improving safety profiles, particularly in elderly patients and those with comorbidities.

Despite these promising attributes, several challenges remain that must be addressed to facilitate clinical translation. The lack of well-designed clinical trials, issues related to extract standardization, limited understanding of gout-specific mechanistic pathways, and concerns regarding long-term stability warrant



further investigation. Future research should focus on conducting randomized controlled trials to establish clinical efficacy, developing validated standardization protocols, integrating nanotechnology to enhance bioavailability, and exploring combination strategies with conventional therapies. The development of smart, stimuli-responsive, and personalized emulgel formulations may further optimize therapeutic outcomes and patient compliance.

In conclusion, Harsingar-based emulgels represent a novel, multi-targeted, and patient-friendly therapeutic approach that holds considerable potential for the safe and effective management of gouty inflammation. By bridging traditional ethnomedicinal knowledge with modern pharmaceutical technology, these formulations offer a scientifically validated alternative to conventional gout therapies. Continued research and development efforts are essential to overcome existing challenges and translate this promising herbal therapeutic strategy from bench to bedside, ultimately contributing to improved outcomes and quality of life for patients suffering from gout.

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