

HERBAL ETHOSOMES FOR ENHANCED TOPICAL AND TRANSDERMAL DELIVERY: FORMULATION STRATEGIES, THERAPEUTIC APPLICATIONS, CURRENT ADVANCES, AND FUTURE PERSPECTIVES

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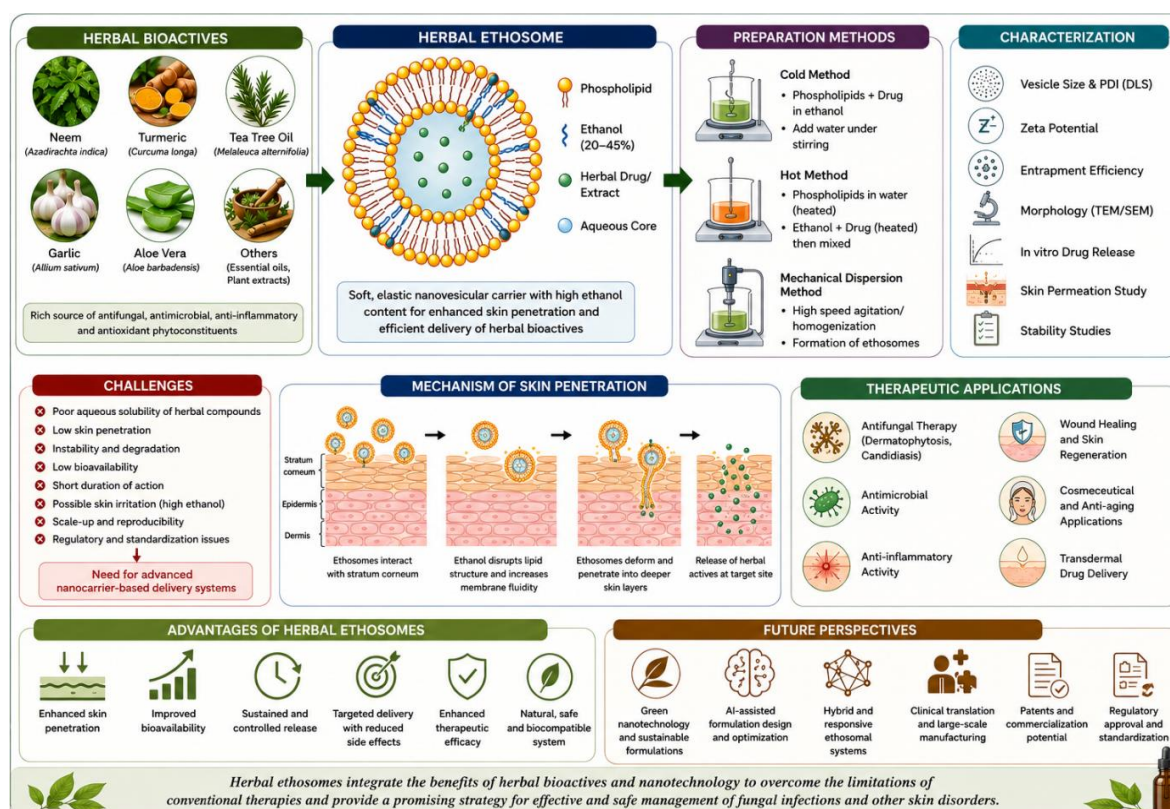
ABSTRACT

Herbal medicines have received significant attention for treating various skin disorders and fungal infections. This interest stems from their effectiveness, natural origin, and good safety profile. However, many plant compounds have poor water solubility, low stability, limited ability to penetrate the skin, and low bioavailability. These factors limit their effectiveness in clinical settings. Ethosomes are carriers made from phospholipids and contain a high level of ethanol. They have emerged as promising nanocarriers that can improve the delivery of herbal bioactive compounds through the skin. The unique structure of ethosomes enhances their flexibility and skin penetration. This helps deliver both water-soluble and fat-soluble plant compounds into deeper layers of the skin. This review outlines the key aspects of herbal ethosomes. It covers their composition, preparation methods, how they penetrate the skin, characterization techniques, and therapeutic uses. Recent developments in herbal ethosomal formulations with

ingredients like curcumin, neem, tea tree oil, aloe vera, garlic, and other plant-derived compounds are discussed. The focus is on their improved antifungal, antimicrobial, anti-

inflammatory, and skin-related effects. Additionally, the review highlights current challenges. These include issues with formulation stability, large-scale manufacturing, regulatory concerns, and clinical application. Emerging trends such as Quality-by-Design, green nanotechnology, hybrid vesicular systems, and formulation development using artificial intelligence are also examined. Overall, herbal ethosomes present a promising method for enhancing the delivery, availability, and effectiveness of herbal medicines. They show great potential for future use in pharmaceuticals and skin-care products.

Graphical Abstract



KEYWORDS: [Herbal ethosomes, nanovesicular carriers, topical drug delivery, transdermal delivery, phytoconstituents, skin permeation, herbal nanotechnology, antifungal therapy].

1. INTRODUCTION

The growing demand for effective, safe, and patient-friendly drug delivery systems has spurred the development of new nanocarrier technologies for topical and transdermal uses. Among the various ways to deliver drugs, the skin provides a non-invasive and convenient option for both local and systemic treatment. Topical and transdermal drug delivery systems offer several advantages. They avoid first-pass metabolism, reduce gastrointestinal breakdown,

provide sustained therapeutic action, and improve patient adherence. However, the highly organized lipid structure of the stratum corneum serves as a significant barrier to drug absorption, greatly limiting the bioavailability of many therapeutic agents (Kang et al., 2024).

In recent years, herbal medicines have gained significant scientific and commercial attention due to their diverse pharmacological activities. These include antifungal, antimicrobial, anti-inflammatory, antioxidant, wound-healing, and anticancer properties. Compounds derived from plants, such as curcumin, quercetin, eugenol, thymol, berberine, resveratrol, and different essential oils, have shown promising potential for treating dermatological disorders and systemic diseases.

Despite their therapeutic benefits, many plant compounds face challenges. They often have poor water solubility, low chemical stability, inadequate skin absorption, rapid degradation, and limited bioavailability, which restricts their clinical effectiveness (Talebi et al., 2025; Hajialyani et al., 2018). Nanotechnology-based drug delivery systems have emerged as an effective strategy to overcome these limitations. Various nanocarriers, including liposomes, niosomes, transfersomes, nanoemulsions, solid lipid nanoparticles, nanostructured lipid carriers, and ethosomes, have been extensively investigated for enhancing the delivery of bioactive molecules across biological barriers. Among these systems, ethosomes have gained particular attention due to their unique composition and superior skin penetration capabilities. Ethosomes are soft, malleable phospholipid vesicles containing relatively high concentrations of ethanol, typically ranging from 20–45%, which significantly enhances vesicle deformability and facilitates deeper penetration through the stratum corneum. (Erdoğar et al., 2025).

The interaction between ethanol and phospholipid bilayers allows ethosomes to disrupt the lipid organization of the skin barrier and improve vesicular flexibility. This mechanism supports effective delivery of both water-soluble and fat-soluble molecules into deeper skin layers and the bloodstream. As a result, ethosomal systems have been researched for delivering antifungal, antimicrobial, anti-inflammatory, pain-relieving, anticancer, and cosmetic agents (Almuqbil&Aldhubiab, 2025).

The combination of herbal bioactive compounds with ethosomal vesicles has led to the creation of herbal ethosomes. This promising nanovesicular platform merges the benefits of plant medicines with the better delivery characteristics of ethosomal technology. Several

studies show that encasing herbal extracts and their active components in ethosomal systems boosts drug retention, stability, controlled release, skin absorption, and effectiveness compared to traditional herbal formulations. Herbal ethosomal formulations with curcumin, neem extract, tea tree oil, aloe vera, eugenol, thymol, garlic extract, and other plant substances have shown positive results for treating fungal infections, inflammatory skin conditions, wound healing, acne, psoriasis, and cosmetic uses (Chauhan et al., 2025).

Recent advancements in pharmaceutical nanotechnology have widened the possibilities for herbal ethosomes. New trends include applying Quality-by-Design (QbD) principles, using artificial intelligence for formulation optimization, developing machine learning prediction models, employing green nanotechnology, and creating hybrid nanocarrier systems that combine ethosomes with hydrogels, nanoemulsions, transfersomes, and polymeric nanoparticles. These innovations aim to enhance formulation stability, manufacturing scalability, effectiveness, and regulatory compliance while helping translate lab research into useful clinical products (Vora et al., 2023; Chauhan et al., 2025; Jadhav et al., 2024).

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nanotechnology, and creating hybrid nanocarrier systems that combine ethosomes with hydrogels, nanoemulsions, transfersomes, and polymeric nanoparticles. These innovations aim to enhance formulation stability, manufacturing scalability, effectiveness, and regulatory compliance while helping translate lab research into useful clinical products (Vora et al., 2023; Chauhan et al., 2025; Jadhav et al., 2024). Despite significant advancements, challenges remain, such as long-term stability, large-scale production, consistency, regulatory standards, and clinical validation. Overcoming these hurdles is crucial for the successful market launch of herbal ethosomal products and their integration into current pharmaceutical and cosmetic practices (Sahoo&Manchikanti, 2013).

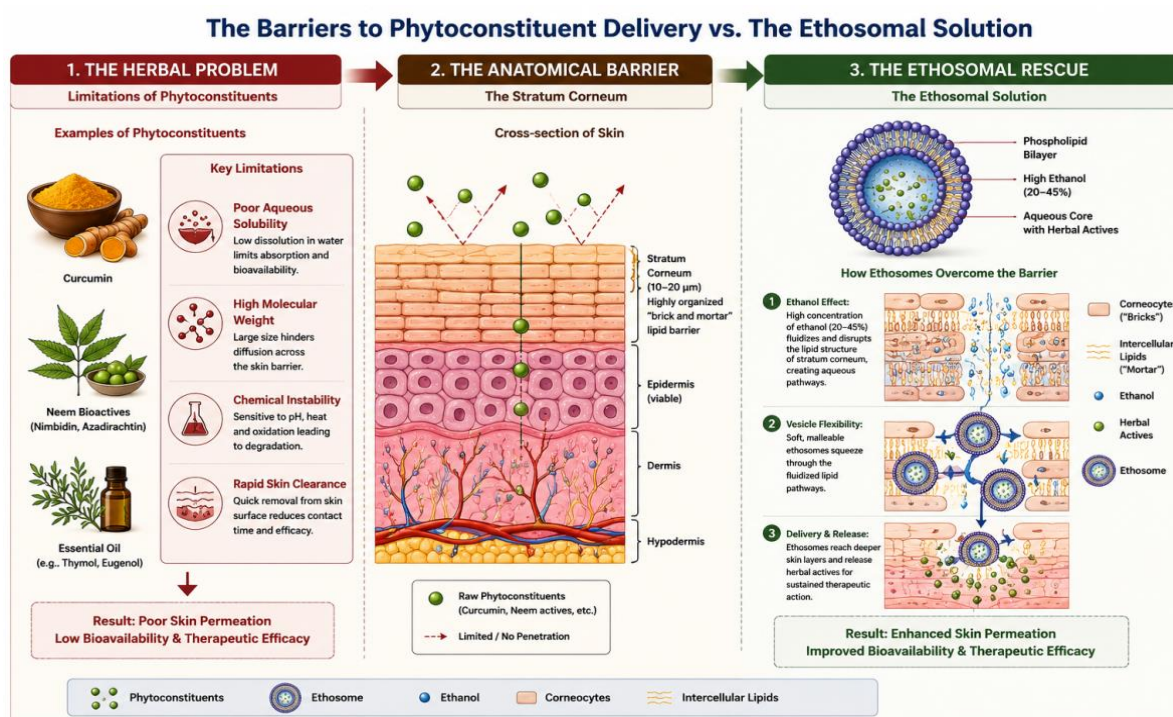


Figure 1: Schematic representation of the limitations of phytoconstituent delivery and the role of herbal ethosomes in enhancing skin permeation and therapeutic efficacy.

2. HERBAL ETHOSOMES: CONCEPTUAL EVOLUTION AND THERAPEUTIC RATIONALE

The development of sophisticated vesicular drug delivery methods has been prompted by the shortcomings of traditional topical formulations and the growing need for effective phytoconstituent administration. Nanocarriers like liposomes, niosomes, transfersomes, and ethosomes have been thoroughly studied over the past few decades to increase the skin penetration and bioavailability of medicinal substances. Because of their high ethanol content and exceptional deformability, which enable improved penetration into the stratum corneum,

ethosomes have become one of these systems' most promising carriers (Gomathi *et al.*, 2026).

Herbal ethosomes, which combine the therapeutic advantages of phytoconstituents with the permeation-enhancing qualities of ethosomal carriers, are the result of the incorporation of herbal bioactive chemicals into ethosomal vesicles. Curcumin, quercetin, eugenol, thymol, resveratrol, neem extract, and tea tree oil are examples of herbal actives that frequently show poor solubility, low skin permeability, and limited bioavailability. The stability, skin penetration, controlled release behavior, and therapeutic efficacy of ethosomes are all enhanced by encapsulation (Madhunithya *et al.*, 2020).

Herbal ethosomes are attractive candidates for the treatment of fungal infections, inflammatory skin disorders, wound healing, acne, psoriasis, and cosmetic applications due to their superior flexibility, enhanced dermal deposition, and improved transdermal delivery when compared to conventional creams, liposomes, and transfersomes (Kusumawati *et al.*, 2023).

2.1 Evolution of Vesicular Drug Delivery System

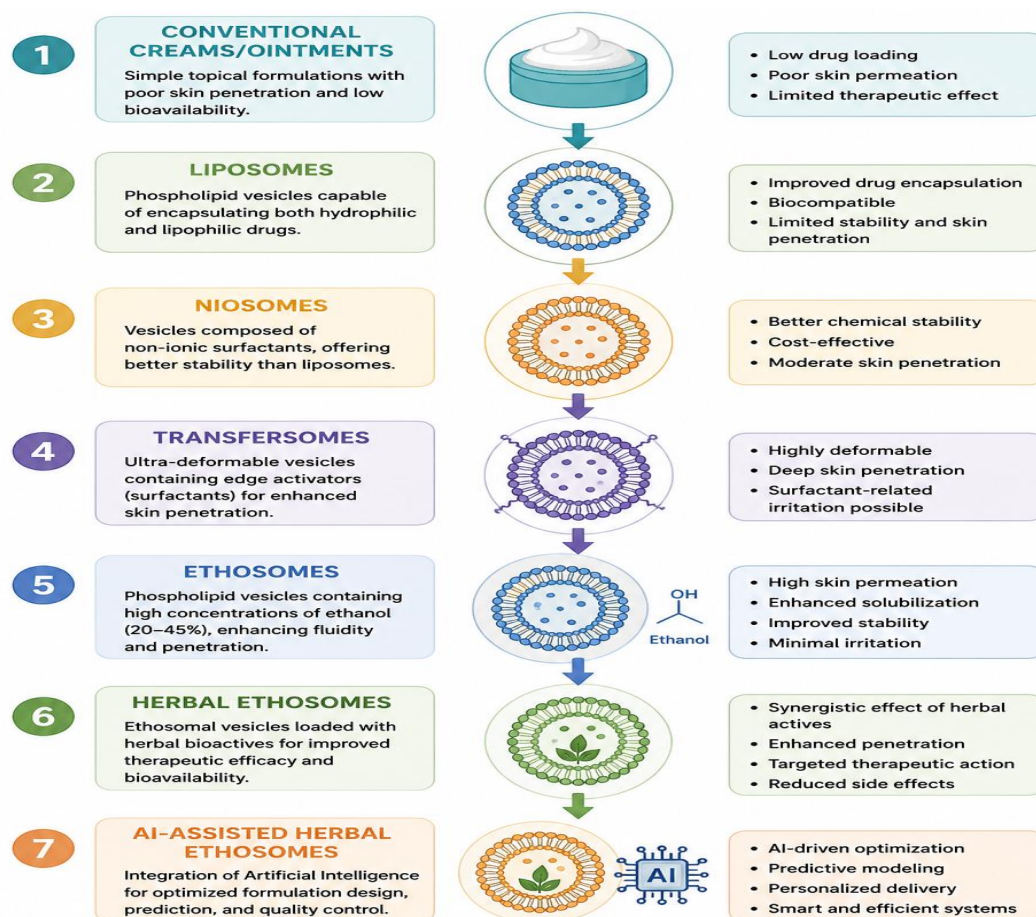


Figure 2: Evolution of Vesicular Drug Delivery Systems.

Table 1: Comparative Overview of Vesicular Carrier Systems.

Carrier System	Major Components	Skin Penetration	Suitability for Herbal Actives
Creams/Ointments	Oils, water, emulsifiers	Low	Poor
Liposomes	Phospholipids + Water	Moderate	Moderate
Niosomes	Nonionic surfactants	Moderate	Good
Transfersomes	Phospholipids + Edge Activators	High	Good
Ethosomes	Phospholipids + Ethanol	Very High	Excellent
Herbal Ethosomes	Ethosomes + Phytoconstituents	Excellent	Excellent

3. COMPOSITION, STRUCTURAL ORGANIZATION, AND CLASSIFICATION OF HERBAL ETHOSOMES

Herbal ethosomes are sophisticated phospholipid-based nanovesicular systems made of ethanol, water, phospholipids, and bioactive substances found in herbs. Ethosomes differ from traditional liposomes due to their high ethanol concentration (20–45%), which also greatly enhances their deformability, stability, and skin penetration capacities. While ethanol enhances permeability, increases membrane fluidity, and improves phytoconstituent solubility, phospholipids form the vesicular bilayer structure. Herbal bioactives may be localized at the lipid–water interface, integrated into the phospholipid bilayer, or confined within the aqueous core, depending on their physicochemical properties. To maximize vesicle stability, drug loading, and transdermal delivery performance, additional excipients such as cholesterol, charge-inducing agents, and edge activators are commonly included (Mahajan *et al.*, 2026).

3.1 Structural Organization of Herbal Ethosomes

The self-assembly of phospholipids into bilayer vesicles in a hydro-ethanolic environment controls the structural structure of herbal ethosomes. While lipophilic substances like curcumin, thymol, and eugenol are integrated into the hydrophobic phospholipid bilayer, hydrophilic phytoconstituents are mainly contained within the watery core. At the lipid–water interface, amphiphilic molecules may separate. While charged compounds like dicetyl phosphate and stearylamine improve colloidal stability by avoiding vesicle aggregation, cholesterol is frequently added to increase membrane stiffness and reduce medication leakage (Kumar *et al.*, 2025).

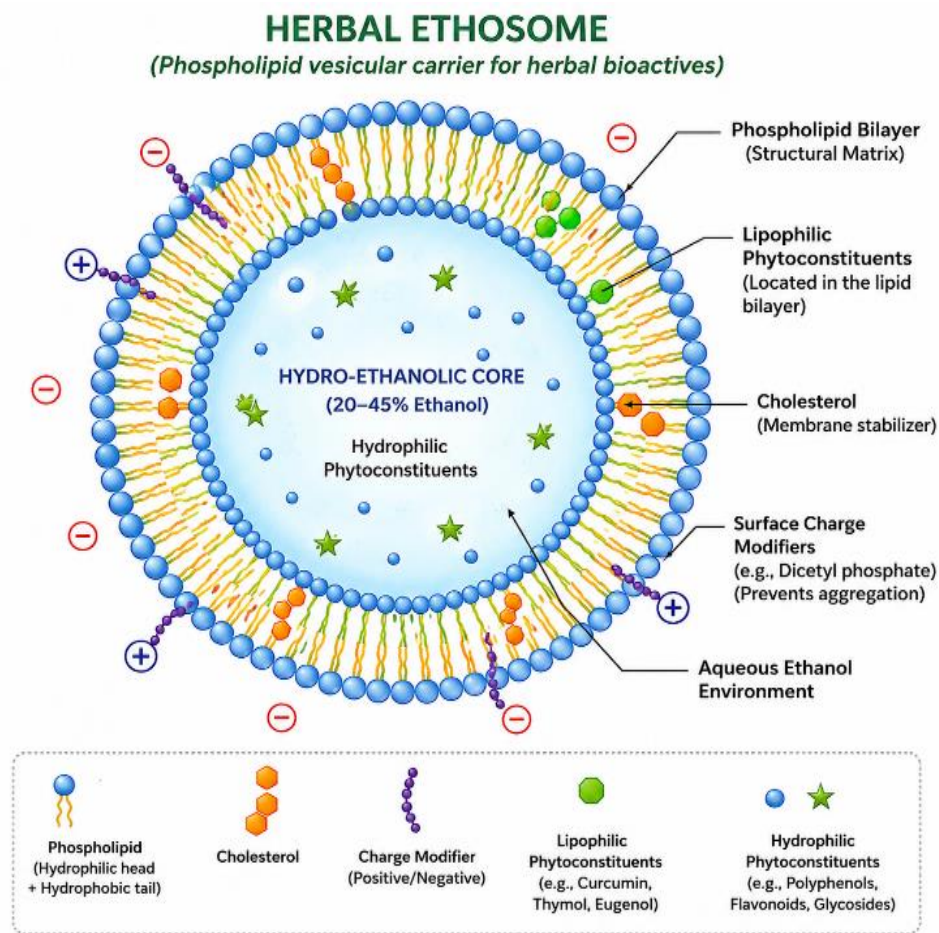


Figure 3: Structural Organization of a Herbal Ethosome.

3.2 Classification of Ethosomal Systems

Based on compositional modifications, ethosomal systems are classified into classical ethosomes, binary ethosomes, and transethosomes.

3.2.1 Classical Ethosomes

Classical ethosomes consist of phospholipids, ethanol, and water. Their simple composition provides improved skin permeation and enhanced delivery of both hydrophilic and lipophilic phytoconstituents compared with conventional liposomes. (Munde et al., 2024).

3.2.2 Binary Ethosomes

Binary ethosomes contain an additional alcohol, such as propylene glycol or isopropyl alcohol, alongside the conventional ethosomal components. The secondary alcohol improves formulation stability, drug solubilization, and storage characteristics, making these systems suitable for complex herbal extracts.

3.2.3 Transethosomes

Transethosomes are hybrid vesicular systems composed of phospholipids, ethanol, and edge activators such as Tween 80, Span 80, or sodium cholate. These additives impart exceptional deformability to the vesicles, enabling deeper skin penetration and improved transdermal transport of phytoconstituents, including high-molecular-weight bioactives (Jain *et al.*, 2012).

Table 2: Classification of Ethosomal Systems.

Type	Composition	Key Characteristics	Major Advantages
Classical Ethosomes	Phospholipids + Ethanol + Water	Conventional ethosomal vesicles	Improved skin permeation
Binary Ethosomes	Classical ethosomes + Secondary alcohol	Enhanced stability and solubilization	Suitable for complex herbal extracts
Transethosomes	Ethosomes + Edge activators	Ultra-deformable vesicles	Superior transdermal delivery

Table 3: Major Components of Herbal Ethosomes and Their Functions.

Component	Examples	Function
Phospholipids	Soy PC, Egg PC	Vesicle formation and drug encapsulation
Ethanol	20–45%	Membrane fluidization and permeation enhancement
Water/Buffer	Purified water, PBS	Vesicle hydration
Herbal Bioactives	Curcumin, Quercetin, Neem extract	Therapeutic activity
Cholesterol	Cholesterol	Membrane stabilization
Charge Modifiers	Dicetyl phosphate, Stearylamine	Prevention of aggregation
Edge Activators	Tween 80, Span 80, Sodium cholate	Enhanced deformability

4. MECHANISMS OF SKIN PENETRATION AND TRANSDERMAL DELIVERY

The synergistic interaction between ethanol and phospholipid vesicles is the main reason for herbal ethosomes' enhanced delivery effectiveness. In contrast to traditional liposomes, ethosomes have a comparatively high ethanol concentration (20–45%), which improves vesicle flexibility while also altering the stratum corneum's barrier characteristics. This dual-action process improves bioavailability and therapeutic efficacy by facilitating the effective transport of encapsulated phytoconstituents into deeper skin layers. (Devaki and others, 2023)

4.1 Ethanol-Mediated Modulation of the Stratum Corneum

The main obstacle to topical and transdermal medication administration is the stratum corneum. When ethanol interacts with the stratum corneum's highly organized intercellular

lipid domains, it disrupts their packing arrangement and increases the fluidity of the membrane. Both hydrophilic and lipophilic phytoconstituents can penetrate more easily thanks to this reversible lipid disturbance, which also lowers barrier resistance and produces temporary diffusion channels. Additionally, ethanol increases the solubility of many herbal chemicals that are weakly soluble in water, which facilitates their integration into the vesicular system.(Crasta and others, 2025).

4.2 Vesicle Deformability and Deep Skin Transport

Vesicle flexibility and deformability are greatly increased when ethanol is incorporated into the phospholipid bilayer. Deeper penetration into the viable epidermis and dermis is made possible by these flexible vesicles' ability to change shape and pass through intercellular channels that are smaller than their own diameter. As a result, when compared to traditional topical carriers, herbal ethosomes obtain more skin deposition and longer phytoconstituent retention (Desai et al., 2026).

4.3 Penetration Pathways of Herbal Ethosomes

There are several complementary methods that herbal ethosomes enter the skin, such as:

- Diffusion via lipid-rich gaps between corneocytes is the intercellular pathway.
- Transcellular pathway: movement between intracellular domains and corneocytes.
- Transappendageal pathway: penetration through sweat glands and hair follicles, which could be significant reservoirs for prolonged drug release.

These routes work together to increase skin deposition, regulated release, and the therapeutic efficacy of encapsulated herbal bioactives. Herbal ethosomes are extremely promising carriers for the delivery of phytoconstituents in dermatological and transdermal applications because of the combined effects of ethanol-induced lipid fluidization and vesicle deformability, which allow them to overcome the drawbacks of traditional topical formulations. (Jacob & Nair, 2026; Mahajan et al., 2026).

Mechanism of Skin Penetration and Transdermal Delivery of Herbal Ethosomes

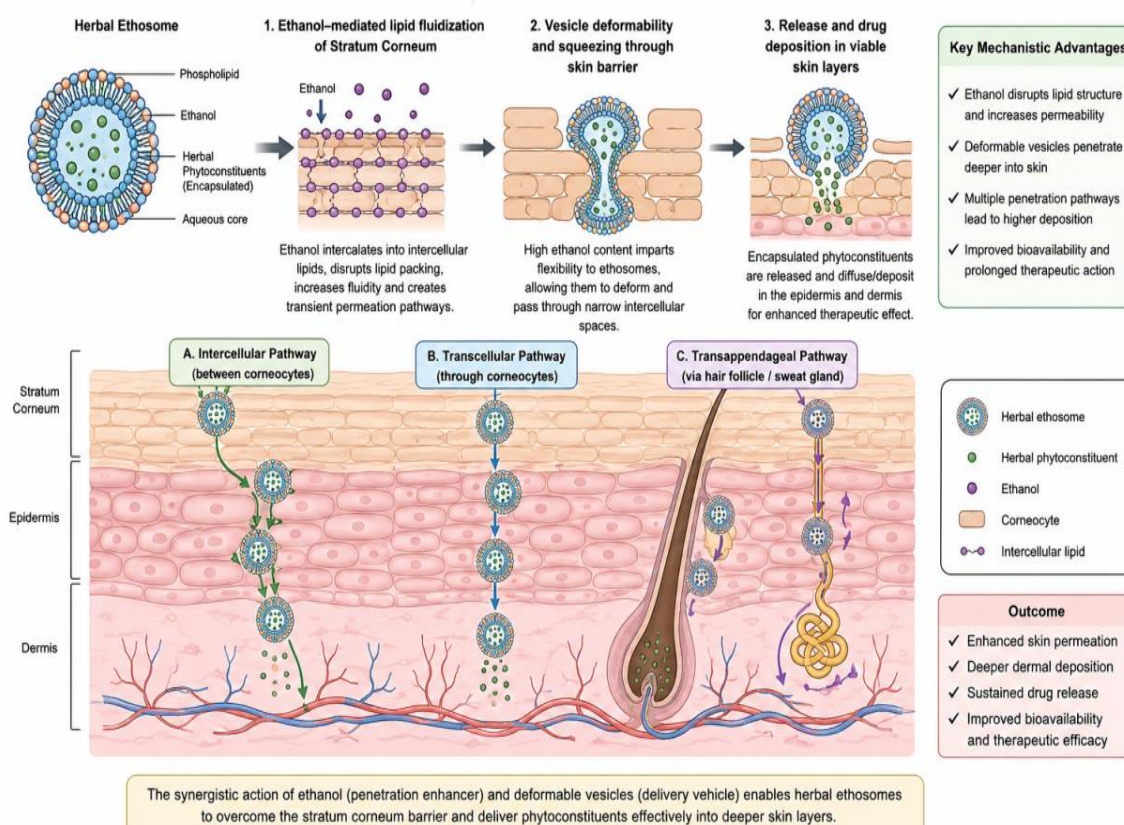


Figure 4: Mechanism of skin penetration and transdermal delivery of herbal ethosomes showing ethanol-mediated lipid fluidization, vesicle deformability, and transport through intercellular, transcellular, and transappendageal pathways.

5. FORMULATION STRATEGIES AND PREPARATION METHODS OF HERBAL ETHOSOMES

The careful selection of phytoconstituents, vesicular components, and fabrication methods are critical to the successful production of herbal ethosomes. The majority of plant-derived bioactives have low bioavailability, quick degradation, restricted skin permeability, and poor water solubility, all of which limit their therapeutic efficacy in traditional topical formulations. By increasing solubility, shielding phytoconstituents from deterioration, and promoting cutaneous and transdermal transport, ethosomal encapsulation has been a successful tactic to get over these restrictions. (Kadam & Tare, 2026).

5.1 Selection of Herbal Bioactives

A wide variety of plant extracts and herbal chemicals have been effectively integrated into ethosomal systems to treat wound healing, psoriasis, acne, microbial infections, inflammatory

disorders, and cosmetic issues. The physicochemical properties, therapeutic target, and compatibility with the phospholipid–ethanol matrix are the main factors that influence the choice of phytoconstituent. (Singh *et al.*, 2022).

Table 4: Representative Herbal Bioactives Incorporated into Ethosomal Systems and Their Reported Outcomes.

Herbal Bioactive / Extract	Therapeutic Application	Reported Outcome in Ethosomal Formulation
Curcumin	Anti-inflammatory, wound healing, psoriasis	Improved skin permeation and bioavailability
Curcuma heyneana Extract	Transdermal delivery	Superior penetration compared with liposomes
Quercetin	Antioxidant, anti-inflammatory	Enhanced dermal deposition and sustained release
Berberine	Antimicrobial, wound healing	Improved skin retention and therapeutic efficacy
Eugenol	Analgesic, antimicrobial	Enhanced penetration and antimicrobial activity
Thymol	Antifungal therapy	Increased skin permeation and antifungal effectiveness
Neem Extract	Acne and skin infections	Enhanced antimicrobial activity and skin deposition
Aloe vera Extract	Wound healing	Improved healing and tissue regeneration
Tea Tree Oil	Acne vulgaris	Improved skin retention and antibacterial action
Garlic Extract	Antifungal therapy	Enhanced antifungal efficacy
Green Tea Polyphenols	Anti-aging and antioxidant applications	Increased stability and dermal delivery
Resveratrol	Anti-aging and photoprotection	Enhanced skin permeation and antioxidant activity
Nigella sativa Extract	Anti-inflammatory and wound healing	Improved therapeutic effectiveness
Centella asiatica Extract	Skin regeneration	Enhanced collagen synthesis and tissue repair
Polyherbal Extracts	Hair growth promotion	Improved follicular delivery and therapeutic response

5.2 Selection of Formulation Components

Vesicle size, entrapment effectiveness, stability, deformability, and epidermal penetration are all strongly influenced by the makeup of herbal ethosomes. The physicochemical properties of the encapsulated phytoconstituent should guide the choice of phospholipids, ethanol concentration, aqueous phase, and auxiliary excipients. (Vishwakarma *et al.*, 2025).

Table 5: Functional Components of Herbal Ethosomal Formulations.

Component	Common Materials Used	Primary Function
Phospholipids	Soy phosphatidylcholine, Egg phosphatidylcholine, Hydrogenated phosphatidylcholine	Vesicle formation, drug encapsulation, membrane flexibility
Ethanol	20–45% Ethanol	Enhances skin permeation, increases membrane fluidity, improves phytoconstituent solubility
Aqueous Phase	Purified water, phosphate buffer	Hydration medium and vesicle stabilization
Cholesterol	Cholesterol	Improves membrane rigidity and reduces drug leakage
Polyols	Propylene glycol, Glycerol	Co-solvent, humectant, stability enhancer
Charge-Inducing Agents	Dicetyl phosphate, Stearylamine	Prevent vesicle aggregation through electrostatic repulsion
Edge Activators*	Tween 80, Span 80, Sodium cholate	Increase deformability and penetration (mainly in transethosomes)

5.3 Preparation Methods of Herbal Ethosomes

The physicochemical properties, encapsulation effectiveness, stability, and skin penetration performance of herbal ethosomes are all strongly influenced by the preparation technique. Numerous manufacturing techniques have been documented; the choice is mostly based on the phytoconstituent's physicochemical characteristics, the intended vesicle size, and the need for scalability. While cutting-edge technologies like microfluidics and high-pressure homogenization are garnering interest for industrial-scale manufacturing, the most widely used techniques include the cold method, hot method, thin-film hydration technique, and ethanol injection method. (Kamaleshwari et al., 2026).

5.3.1 Cold Method

Due to its ease of use and compatibility with thermolabile phytoconstituents, the cold approach is the most used method for making herbal ethosomes. This approach involves dissolving phospholipids and herbal bioactives in ethanol, then gradually adding the aqueous phase while stirring constantly. To decrease vesicle size, the resulting vesicular dispersion is then homogenized or sonicated. For sensitive phytochemicals like curcumin, quercetin, and polyphenolic compounds, this method is preferable because it reduces heat degradation. (Manpreet et al., 2025).

5.3.2 Hot Method

The hot approach entails producing the ethanolic and aqueous phases independently at high temperatures, usually about 40°C, and then combining them under carefully monitored circumstances. For extremely lipophilic herbal extracts that need heat help to fully dissolve, this method is beneficial. However, when dealing with phytoconstituents that are sensitive to heat, its use can be restricted. (Pandey et al., 2014).

5.3.3 Thin-Film Hydration Method

The thin-film hydration method uses solvent evaporation to create a thin phospholipid film, which is then hydrated with the herbal bioactive in a hydro-ethanolic solution. This technique often yields formulations with high encapsulation effectiveness and consistent particle size distribution, and it provides good control over vesicle composition. As a result, it is frequently employed in the development of herbal ethosomes on a research scale. (Huanbutta et al., 2022).

5.3.4 Ethanol Injection Method

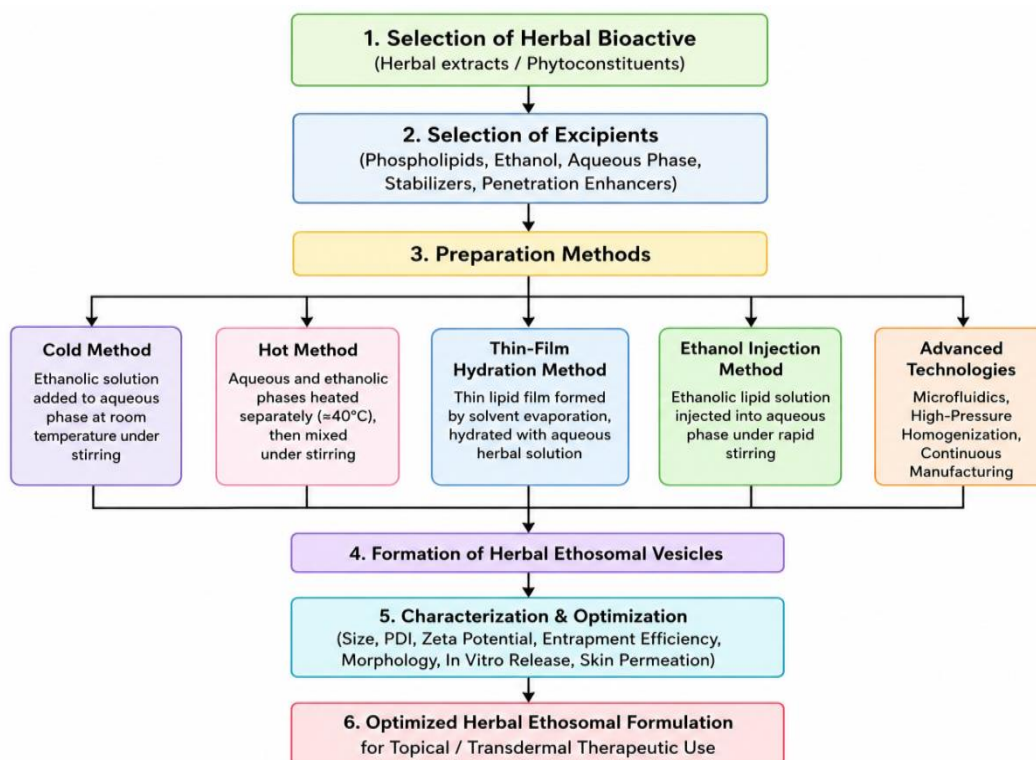
The ethanol injection method involves continuously stirring an ethanolic lipid solution while it is injected into an aqueous phase. Spontaneous vesicle formation is encouraged by ethanol's quick diffusion into the aqueous solution. This technique produces relatively small vesicles with narrow size distributions and is straightforward and repeatable. (Du & Sun, 2023).

5.3.5 Advanced Fabrication Technologies

High-pressure homogenization, microfluidic technologies, and continuous manufacturing platforms for ethosome synthesis have all been made possible by recent developments in nanotechnology. When compared to traditional batch manufacturing techniques, these methods provide better process control, increased scalability, and improved reproducibility. It is anticipated that the integration of Quality-by-Design (QbD) principles and AI-assisted process optimization will enhance formulation development and make the industrial translation of herbal ethosomal products easier. (Guo et al., 2025)

Table 6: Comparison of Preparation Methods for Herbal Ethosomes.

Method	Principle	Major Advantages	Limitations
Cold Method	Hydration of ethanolic lipid phase at room temperature	Simple, suitable for thermolabile phytoconstituents	Limited scalability
Hot Method	Mixing of heated aqueous and ethanolic phases	Useful for lipophilic extracts	Possible degradation of heat-sensitive compounds
Thin-Film Hydration	Hydration of solvent-evaporated lipid film	High encapsulation efficiency and vesicle uniformity	Time-consuming process
Ethanol Injection	Injection of ethanolic lipid solution into aqueous phase	Produces small vesicles and good reproducibility	Requires precise process control
High-Pressure Homogenization	Mechanical size reduction under high pressure	Scalable and uniform vesicle production	High equipment cost
Microfluidics	Controlled microscale mixing of phases	Excellent reproducibility and narrow size distribution	Specialized instrumentation required

**Figure 5: Schematic representation of the formulation and fabrication strategies employed in herbal ethosome development.**

6. CHARACTERIZATION TECHNIQUES OF HERBAL ETHOSOMES

To determine vesicle quality, stability, drug-loading capacity, and transdermal function, herbal ethosomes must be characterized. According to recent research, ethosomal vesicles can range in size from 50 to 400 nm; formulations less than 300 nm often show better dermal deposition and skin penetration. A homogeneous vesicular population that is appropriate for topical application is indicated by a PDI < 0.30.(Barupal et al., 2011; Huanbutta et al., 2022; Mahajan et al., 2026).

6.1 Vesicle Size, PDI, and Zeta Potential

Vesicle size, size distribution, and surface charge are frequently measured using dynamic light scattering (DLS). The zeta potential values of the majority of improved herbal ethosomes range from -20 to -50 mV, indicating sufficient electrostatic stability and decreased vesicle aggregation during storage.(Pandey et al., 2014; Desai et al., 2026).

6.2 Entrapment Efficiency and Drug Loading

One important measure of formulation performance is entrapment efficiency (EE%). Depending on the physicochemical properties of the encapsulated phytoconstituent and formulation composition, recent herbal ethosomal formulations have reported EE values ranging from 70 to 95%. For bioactives that are poorly soluble in water, such curcumin, quercetin, thymol, and eugenol, high EE is especially beneficial. (Huanbutta et al., 2022).

6.3 Morphological and Structural Characterization

Atomic force microscopy (AFM), scanning electron microscopy (SEM), and transmission electron microscopy (TEM) are frequently used to verify vesicle morphology. Herbal ethosomes are typically spherical, smooth-surfaced, unilamellar or multilamellar vesicles with nanoscale dimensions. Drug encapsulation, compatibility, and changes in crystallinity after vesicle formation are further confirmed by FTIR, DSC, and XRD investigations.(Barupal et al., 2011; Huanbutta et al., 2022;Vishwakarma et al., 2025).

6.4 In Vitro Release and Skin Permeation Studies

The most used technique for assessing drug release and skin penetration is still Franz diffusion cell investigations. Herbal ethosomes have shown a 1.5–5-fold increase in skin penetration and a much higher dermal retention of phytoconstituents when compared to traditional formulations, which has increased therapeutic efficacy.(Huanbutta et al., 2022; Mahajan et al., 2026).

6.5 Stability Assessment

To track changes in vesicle size, zeta potential, entrapment efficiency, and ethanol concentration during storage, stability tests are carried out. Under refrigeration, optimized formulations usually keep more than 80% of their original drug content and have adequate physicochemical stability for several months. (Pandey *et al.*, 2014).

Table 7: Key Characterization Parameters of Herbal Ethosomes.

Parameter	Preferred Range/Outcome	Significance
Vesicle Size	50–400 nm	Skin penetration efficiency
PDI	< 0.30	Formulation uniformity
Zeta Potential	–20 to –50 mV	Colloidal stability
Entrapment Efficiency	70–95%	Drug-loading capacity
Morphology	Spherical vesicles	Structural integrity
Skin Permeation	1.5–5-fold enhancement	Improved transdermal delivery
Stability	>80% drug retained	Shelf-life performance

7. Therapeutic Applications Of Herbal Ethosomes

Incorporating phytoconstituents into ethosomal nanocarriers has been a successful method for addressing the low bioavailability, restricted skin penetration, and poor water solubility that are frequently linked to herbal remedies. Herbal ethosomes enable improved skin deposition, extended retention, and regulated release of bioactive chemicals due to their ethanol-rich and highly deformable vesicular structure.

Fungal infections, bacterial skin illnesses, wound healing, inflammatory dermatoses, psoriasis, acne vulgaris, and cosmeceutical interventions are only a few of the dermatological uses for which recent studies have shown their potential. Herbal ethosomes often show better skin penetration, higher local medication concentrations, and better therapeutic results when compared to traditional lotions, ointments, and gels.

7.1 Antifungal Applications

The most researched use of herbal ethosomes is still antifungal therapy. Essential oils, phenolics, and terpenoids are examples of plant-derived antifungal chemicals that frequently show insufficient penetration into affected skin layers. The transport of these substances through the stratum corneum is improved by ethosomal encapsulation, which also encourages long-lasting antifungal action.

The ability of ethosomes to deliver therapeutic phytoconstituents directly into deeper, heavily colonized skin layers was demonstrated by the ethosomal formulation of Zingiber zerumbet

rhizome extract, which showed significantly improved skin deposition and enhanced antifungal efficacy against cutaneous fungal infections.

7.2 Antimicrobial and Anti-Acne Applications

Neem extract, tea tree oil, berberine, eugenol, and thymol are examples of herbal bioactives with broad-spectrum antibacterial activity. However, quick volatilization and inadequate skin penetration frequently limit their therapeutic efficacy.

By better localizing these substances within pilosebaceous units and diseased tissues, ethosomal delivery systems increase antibacterial action and lower the local microbial burden. For the treatment of acne vulgaris, where both focused antibacterial action and anti-inflammatory actions are simultaneously needed to cure lesions, these systems have drawn more and more interest.

7.3 Wound Healing and Tissue Regeneration

Curcumin, aloe vera, and extracts from *Centella asiatica* are just a few of the herbal substances that have strong anti-inflammatory, tissue-regenerative, and antioxidant qualities. These bioactives' stability and skin retention are improved by ethosomal encapsulation, which leads to increased collagen synthesis, quicker epithelialization, and quicker wound closure. According to recent research, ethosomal administration can greatly enhance the therapeutic efficacy of phytoconstituents that heal wounds as compared to traditional topical formulations. (Huanbutta *et al.*, 2022; Mahajan *et al.*, 2026).

7.4 Anti-Inflammatory and Anti-Psoriatic Applications

Local oxidative stress and dysregulated cytokine production are hallmarks of chronic inflammatory skin conditions such as psoriasis, dermatitis, and eczema. Curcumin, quercetin, resveratrol, and boswellic acids are examples of natural substances that have demonstrated encouraging anti-inflammatory properties. Ethosomal formulations enhance these drugs' skin distribution and local absorption, allowing for more efficient inhibition of inflammatory pathways while reducing undesired systemic exposure.

7.5 Skin Cancer and Cosmeceutical Applications

The ethosomal transport of chemopreventive phytochemicals like curcumin, resveratrol, and epigallocatechin gallate (EGCG) has been investigated recently. Future applications in the prevention and treatment of skin cancer are supported by improved skin penetration, which

raises the local concentrations of these substances within epidermal tissues. Antioxidant-rich herbal ethosomes are also being researched more and more in cosmeceutical formulations for photoprotection, anti-aging, and skin regeneration. (Shi *et al.*, 2025).

Table 8: Representative Herbal Ethosomal Formulations and Therapeutic Applications Reported in Recent Literature.

Herbal Bioactive	Therapeutic Application	Major Findings Reported	Reference
<i>Zingiber zerumbet</i> rhizome extract	Antifungal skin infection	Enhanced skin penetration and antifungal efficacy in deep skin layers	Huanbutta <i>et al.</i> , 2022
Combined herbal extracts	Hair growth promotion	Improved follicular delivery and hair growth activity	Madhunithya <i>et al.</i> , 2020
<i>Curcuma heyneana</i> rhizome extract	Transdermal delivery	Ethosomes showed superior permeation compared with liposomes	Kusumawati <i>et al.</i> , 2023
Curcumin	Wound healing, psoriasis, inflammation	Improved dermal deposition and sustained release	Multiple studies
Quercetin	Anti-inflammatory applications	Enhanced antioxidant and anti-inflammatory activity	Recent nanocarrier studies
Tea tree oil	Acne vulgaris and antimicrobial therapy	Improved skin retention and antibacterial efficacy	Recent ethosomal reports
Neem (<i>Azadirachta indica</i>) extract	Antibacterial and wound healing applications	Enhanced local antimicrobial action	Herbal ethosome studies
Berberine	Acne and skin infections	Improved dermal bioavailability and antibacterial activity	Recent topical nanocarrier studies
Resveratrol	Anti-aging and psoriasis	Increased skin penetration and antioxidant effects	Recent vesicular delivery studies
Aloe vera extract	Wound healing and cosmeceuticals	Improved hydration and tissue regeneration	Herbal delivery studies

8. RECENT ADVANCES AND EMERGING TRENDS

The landscape of herbal ethosomal research is shifting from traditional laboratory methods toward advanced nanomanufacturing platforms to overcome scale-up and stability constraints.

8.1 Quality-by-Design (QbD) and Design of Experiments (DoE)

Critical Quality Attributes (CQAs) such as vesicle size, PDI, and entrapment efficiency are

optimized using mathematical modeling in QbD and DoE frameworks. QbD removes trial-and-error and guarantees regulatory compliance by methodically establishing crucial material and process parameters.

8.2 Artificial Intelligence and Machine Learning

Based on phytoconstituent structures, artificial intelligence (AI) and machine learning (ML) models use artificial neural networks to forecast medication loading, bilayer compatibility, and long-term stability. This computer method significantly shortens optimization times and minimizes material waste.

8.3 Green Nanotechnology

Green nanotechnology uses biodegradable surfactants, renewable plant-derived phospholipids, and energy-efficient processing to promote sustainable production. Chemical residues are reduced and formulation biocompatibility for delicate skin is increased by removing hazardous organic solvents.

8.4 Microfluidics

To accomplish quick, regulated fluid mixing, microfluidic technologies push organic and hydro-ethanolic phases through tiny channels. This method produces extremely uniform nanovesicles with small size distributions and remarkable batch-to-batch reproducibility by avoiding the nonuniformity of batch manufacture.

8.5 Smart/Stimuli-Responsive Ethosomes

In reaction to particular microenvironmental alterations at the affected skin region, stimuli-responsive ethosomes are designed to initiate on-demand medication release. Localized pH changes in psoriatic or tumor tissues, inflammatory temperature increases, and overexpressed microbial enzymes are important triggers. In reaction to particular microenvironmental alterations at the affected skin region, stimuli-responsive ethosomes are designed to initiate on-demand medication release. Localized pH changes in psoriatic or tumor tissues, inflammatory temperature increases, and overexpressed microbial enzymes are important triggers.

8.6 Hybrid Nanocarriers

Hybrid platforms combine ethosomes with advanced materials to optimize topical performance:

- **Ethosomal Hydrogels:** Incorporating ethosomes into polymer networks (e.g., carbopol, chitosan) to increase viscosity, prolong local skin retention, and prevent formulation runoff.
- **Vesicular Hybrids (Transethosomes):** Blending ethosomal ethanol with specialized edge activators to engineer ultra-deformable vesicles that maximize transdermal flux.
- **Polymer-Lipid Hybrids:** Coating vesicles with biocompatible polymers to prevent drug leakage and enhance chemical stability during shelf storage. ((Buya et al., 2024; Babazadeh et al., 2017).

Table 9: Emerging Technical Trends in Herbal Ethosomal Engineering.

Technological Trend	Core Technical Principle	Primary Advantage in Herbal Delivery
QbD& DoE (QbD 4.0)	Statistical design space modeling with multivariate and risk-based analysis	Ensures robust formulation development, regulatory compliance (ICH Q8–Q11), and scalable production
AI & Machine Learning	Deep learning, ANN, and QSAR-based predictive modeling of nanocarrier systems	Enables rapid in-silico optimization, stability prediction, and reduced experimental workload
Green Nanotechnology	Use of bio-derived phospholipids, eco-friendly solvents, and sustainable manufacturing	Minimizes toxicity, improves biocompatibility, and supports sustainable pharmaceutical development
Microfluidics & Continuous Manufacturing	Controlled microscale laminar flow mixing and continuous production systems	Produces uniform vesicles with low PDI, high reproducibility, and industrial scalability
Stimuli-Responsive (Smart) Systems	Triggered release via pH, temperature, enzymes, or ROS in diseased microenvironments	Enables targeted, on-demand drug release with improved therapeutic efficacy
Hybrid Nanocarrier Systems	Combination of ethosomes with hydrogels, transfersomes, liposomes, or polymer coatings	Enhances stability, skin retention, permeability, and controlled drug release
Clinically Translational Platforms	GMP-compatible scalable manufacturing with PK/PD and regulatory alignment	Bridges laboratory-to-clinic gap and improves commercialization potential of herbal nanomedicines

9. CURRENT CHALLENGES, REGULATORY CONSIDERATIONS, AND FUTURE PERSPECTIVES

A complex web of obstacles stands in the way of the transfer of herbal ethosomes from lab-

scale research to commercial medicinal and cosmetic applications. These obstacles include safety concerns about high topical ethanol exposure, technical stability problems brought on by membrane fluidization, and a clear lack of standardized international regulatory frameworks for nano-phytomedicines. In order to address these problems, modern engineering techniques like as continuous microfluidic scale-up, Quality-by-Design (QbD) standardization, and carefully planned human clinical trials must replace traditional batch manufacturing. (Patra, 2025) Table 10 provides a methodical summary of the main obstacles, legal restrictions, and suggested future remedies influencing the clinical translation of herbal ethosomal systems.

Table 10: Challenges, Regulatory Hurdles, and Future Solutions for Herbal Ethosomes.

Category	Key Challenges & Bottlenecks	Proposed Future Solutions
Technical Stability	Ethanol-induced membrane destabilization leading to drug leakage; high batch-to-batch variability due to complex phytochemical composition	Polymer–lipid hybrid coating strategies to enhance vesicle stability; implementation of QbD and DoE for standardization of formulation and extract variability
Regulatory Safety	Potential skin irritation and dryness due to high ethanol content (20–45%); absence of harmonized global regulatory guidelines for nano-herbal systems	Comprehensive long-term dermatological safety and tolerability studies; development of standardized international regulatory frameworks and safety thresholds for nanophytomedicines
Commercialization	Limited scalability from laboratory-scale batches to industrial production; lack of robust clinical and translational human studies	Adoption of continuous manufacturing platforms (e.g., microfluidics-based systems); design of well-structured multicenter clinical trials for regulatory approval and market translation

10. CONCLUSION

A major development in pharmaceutical nanotechnology, herbal ethosomes successfully connect conventional phytomedicine with contemporary tailored topical and transdermal medication delivery. Their distinctive vesicular structure, which combines phospholipids with a high ethanol concentration, gets around some of the main drawbacks of herbal actives, such as poor solubility, chemical instability, quick clearance, and the stratum corneum's barrier function. Together, ethanol-induced lipid fluidization and vesicle deformability improve dermal deposition, increase skin penetration, and allow for the prolonged release of hydrophilic and lipophilic phytoconstituents.

Single-compound encapsulation is clearly giving way to multi-component herbal and polyherbal systems with better stability and therapeutic efficacy, according to recent research trends. However, issues including extract variability, long-term physicochemical stability, and regulatory harmonization continue to be major obstacles to complete clinical translation. By enhancing reproducibility, scalability, and process control, emerging technologies including Quality-by-Design (QbD), artificial intelligence-based formulation optimization, green nanotechnology, and continuous microfluidic manufacturing are tackling these constraints. Furthermore, by improving early-stage safety and permeability assessment, sophisticated *in vitro* skin models are decreasing reliance on traditional animal research. To demonstrate therapeutic superiority, safety, and regulatory acceptability, future clinical translation will rely on well planned multicenter human trials. All things considered, herbal ethosomes show great promise as a biocompatible, effective, and adaptable nanocarrier technology for cosmetic and dermatological uses.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

Authors' Contributions

Author rr designed the review outline, managed the literature searches, and drafted the manuscript. Author kt, author rs, author rr, author gk, author sp, and author gv conducted structural analysis, verified data extraction from recent publications, and carefully reviewed the final layout. All authors read and approved the final manuscript.

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