

HERBAL EXTRACT AS CORE PARTICLE IN ETHOSOME: A REVIEW

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ABSTRACT

Ethosomes are advanced, highly flexible lipid-based vesicular delivery systems made of phospholipids, water and high concentrations of alcohol (20-45% ethanol or isopropyl alcohol). The skin is made up of three primary layers, the epidermis, dermis and hypodermis. The epidermis is made up of 40-50 layers of stacked squamous epithelial cells in the stratum basale, stratum spinosum, stratum granulosum and stratum corneum. Conventional liposomes have limitations in deep delivery, while ethosomes can be used as “push and pull” devices to improve transdermal penetration and intracellular distribution of high molecular weight compounds into these deep epidermal layers. This review aims to provide insight into the classification, preparation techniques, mechanisms of ethosomes and to assess their potential for optimising the transdermal delivery of bioactive herbal extracts. Ethosomes can be classified as classical, binary and trans-ethosomes and are prepared by methods such as thin film hydration, cold, hot, reverse phase evaporation and transmembrane pH gradient techniques. Mechanistically, ethanol acts as a penetration enhancer that fluidizes the lipid barrier of the stratum corneum; when combined with flexible vesicles, ethanol creates a synergistic interaction with skin lipids to drive deep tissue penetration. This appraisal summarise that, ethosomes are better transdermal carriers than conventional liposomes and greatly enhance the bioavailability, analgesic and anti-inflammatory effects of phyto-constituents like wintergreen oil, mentha oil, capsaicin, turmeric, lavender and Nirgundi.

KEYWORDS: Analgesic, anti-inflammatory, ethosome, herbal extract.

INTRODUCTION

Transdermal delivery systems for drugs (TDDSs) are a novel and patient-friendly route for drug administration and have many advantages over conventional oral and parenteral drug delivery routes. They are designed to carry drugs through the skin barrier and into the blood stream, maintaining a steady level of drug over time. They deliver medications directly into the blood stream, thus avoiding the first pass metabolism of the liver and degradation in the gastrointestinal tract.^[1] TDDSs such as patches, gels and vesicular systems such as ethosomes offer flexible administration as compared to oral administration which is more difficult to discontinue. For example, a patch can be removed or an application stopped to quickly halt delivery of the drug. TDDSs are routinely used for the treatment of a wide spectrum of physiological diseases such as neurological, pain management, hormone treatment, vaccine administration and cardiovascular diseases.^[2] This has been made possible by TDDSs that use advanced technology such as

nanoparticles, microneedles and vesicular systems such as ethosomes to enhance drug penetration through the skin by increasing the efficiency of delivery and allowing access to deeper tissues.^[3] However, the use of TDDS is severely limited by the skin's selective permeability despite of many benefits. The stratum corneum layer is the top layer of the epidermis and acts as a barrier to protect the body, allowing only low molecular weight chemicals to pass through.^[4] The penetration and permeation of molecules through the skin are influenced by the molecular mass, melting point, log P, pKa and dosage of a drug.^[5] Thus, only molecules with a mass below 500 daltons and partition-coefficients in a favorable range can efficiently penetrate the skin.^[6] This restriction greatly reduces the efficient distribution of some therapeutic medicines. Moreover, drugs diffuse passively through the skin, so conventional TDDSs make it difficult to rapidly assess drug plasma concentrations. This makes it difficult to give emergency treatment or to treat severe pain. The therapeutic results and absorption

effectiveness of TDDSs^[7] depend on age, skin moisture, the site of drug administration, skin temperature, skin conditions, wounds, and heavy perspiration. Most of the TDDS systems allow the use of a penetration enhancer which could cause irritation to the people with sensitive skin.^[8] Ethanol in ethosomes and certain surfactants and fatty acids used in transdermal drug delivery system (TDDS) formulations, act as penetration enhancers by disrupting the lipid structure of stratum corneum which may cause minor irritation or compromise the outermost barrier of skin.^[9] Ethosome is one of the most promising vesicular nanocarriers developed for transdermal drug delivery. In 1997, Touitou et al.^[10] described a class of lipid-based vesicles called ethosomes.

THE ETHOSOMES

Ethosomes are advanced lipid-based vesicular delivery systems for drugs containing a high concentration of ethanol, which enhances their flexibility and capacity for transdermal penetration compared to conventional liposomes. Ethosomes are predominantly utilised in pharmaceutical applications to improve transdermal drug delivery for systemic and localised therapeutic effects.

They are also studied in cosmetics to promote the penetration of active substances into the upper layers of the skin. In ethosomes, more ethanol is present than in other vesicular systems (liposomes) and therefore ethosomes affect the intracellular level of the stratum corneum and improve penetration.^[11] Ethosomes are one of the most promising vesicular nanocarriers developed for transdermal drug delivery. Ethosomes are lipid-based vesicles, first described in 1997 by Touitou et al.^[12] Ethosomes are soft, flexible lipid vesicles composed of phospholipids, water and alcohol (ethanol or isopropyl alcohol) at relatively high concentrations (20–45%).^[13] The ethosomes can be loaded with hydrophilic, lipophilic or amphiphilic drugs. These can then penetrate into the deeper layers of the skin and into the systemic circulation. Ethosomal systems are different from liposomes in that they contain significant amounts of ethanol in addition to phospholipids and water. Since then, new generations of ethosomal systems have been developed by adding specific chemicals to the basic ethosomal formula in an effort to improve vesicular properties and skin penetration.^[14]

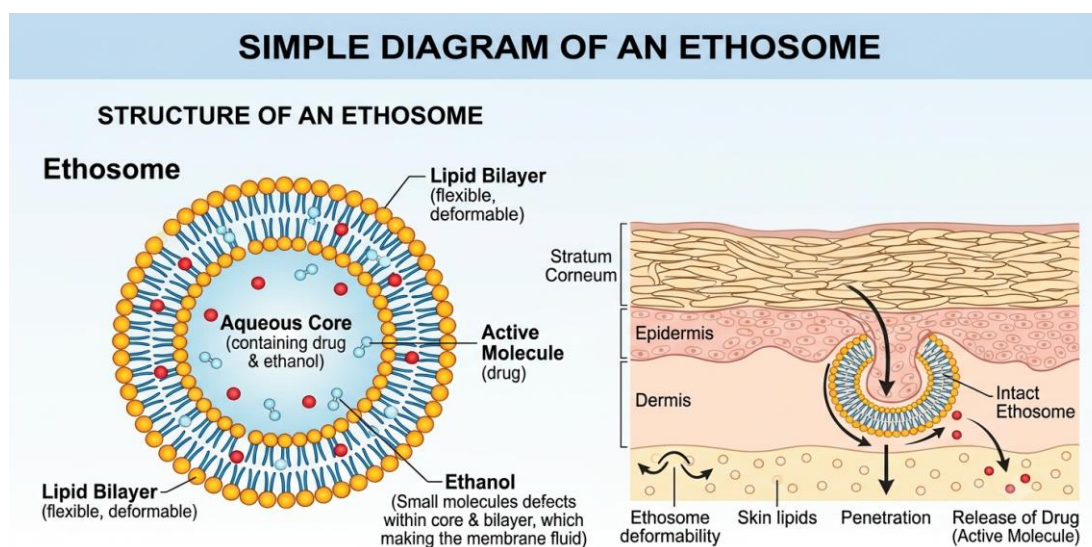


Fig. 1: Structure of ethosome.

Ethosome Benefits^[15]

1. Ethosomes enhance penetration of drugs through the skin for intracellular, transdermal and dermal delivery.
2. Produce diverse compounds with varied physicochemical properties including peptides, proteins, hydrophilic and lipophilic molecules, and other macromolecules.
3. The components of ethosomes are non-toxic, generally recognised as safe (GRAS) and approved for use in medicine and cosmetics.
4. Low risk profile: The toxicity profiles of ethosome are well-documented in the scientific literature, indicating that no significant risk is associated with the ethosome structure in large-scale medication development.
5. Ethosomal system is suitable for instant marketing being non-invasive and passive in nature.
5. Ethosomal delivery systems for drugs may have wide application in the pharmaceutical, biotechnology, veterinary, cosmetic and nutraceutical industries.
6. Excellent patient compliance: The ethosomal drug delivery is in the form of a semi-solid (gel or cream) instead of iontophoresis, sonophoresis and other complicated drug delivery techniques which lead to excellent patient compliance.
7. Ease of industrial scale-up: Ethosome manufacturing requires no complex technological investments and

is comparatively easy to make. It is easy to create multiliter volumes for ethosomal formulation.

8. Ethosomes improve medication penetration through the skin in an effective way, allowing the medicine to enter the bloodstream or reach the intended location in the skin. Drug entrapment efficiencies are higher than those of liposomes.
9. There is outstanding stability over extended periods of time.
10. Since alcohol functions as a natural preservative in ethosomes, no additional preservative is required.
11. Ethosome production is quite inexpensive.
12. Drug transport via the skin is independent of concentration.

Types of Ethosomal Systems

1. Traditional Ethosomes

Phospholipids, water, and a high concentration of ethanol (40%) make up classical ethosomes. Classical ethosomes may capture drugs with molecular weights between 130,077 Da and 24 kDa.^[16]

2. Ethosomes those are binary

By combining a different kind of alcohol with the traditional ethosomes, binary ethosomes may be created. The most often utilised alcohols are isopropyl alcohol (IPA) and propylene glycol (PG).^[16]

3. Transethosomes

It includes a penetration enhancer (surfactant) and fundamental elements from traditional ethosomes.

designed to create transethosomes by combining the benefits of transferosomes with traditional ethosomes. Because they include the benefits of both transferosomes and traditional ethosomes, transethosomes are an advanced form of ethosomes.^[16]

The Ethosomal Drug Delivery System's Mode of Action

It was proposed that ethanol, vesicles, and skin lipids work in concert. An interaction between ethosomes and skin lipids may explain why ethosomes distribute active ingredients more effectively than liposomes. An explanation for this interaction has been put forward.

As shown in Fig. 2, the first part of the mechanism is considered to be related to the ethanol effect, where ethanol interacts with the lipid molecules in the polar head group region to reduce the transition temperature of the lipids in the stratum corneum, increasing their fluidity and reducing the density of the lipid multilayer.^[7] Then, the "ethosome effect" is responsible for the drug release into the deep layers of the skin by lipid penetration and permeation through the creation of new routes caused by the malleability and fusing of ethosomes with skin lipids. Additionally, ethanol may provide vesicles soft, flexible properties that make it easier for them to enter the skin's deeper layers. A fusion of ethosomes with skin lipids and drug release at different stages along the penetration route may subsequently lead to the drug's release in the deep layers of the skin and its transdermal absorption.^{[17],[18]}

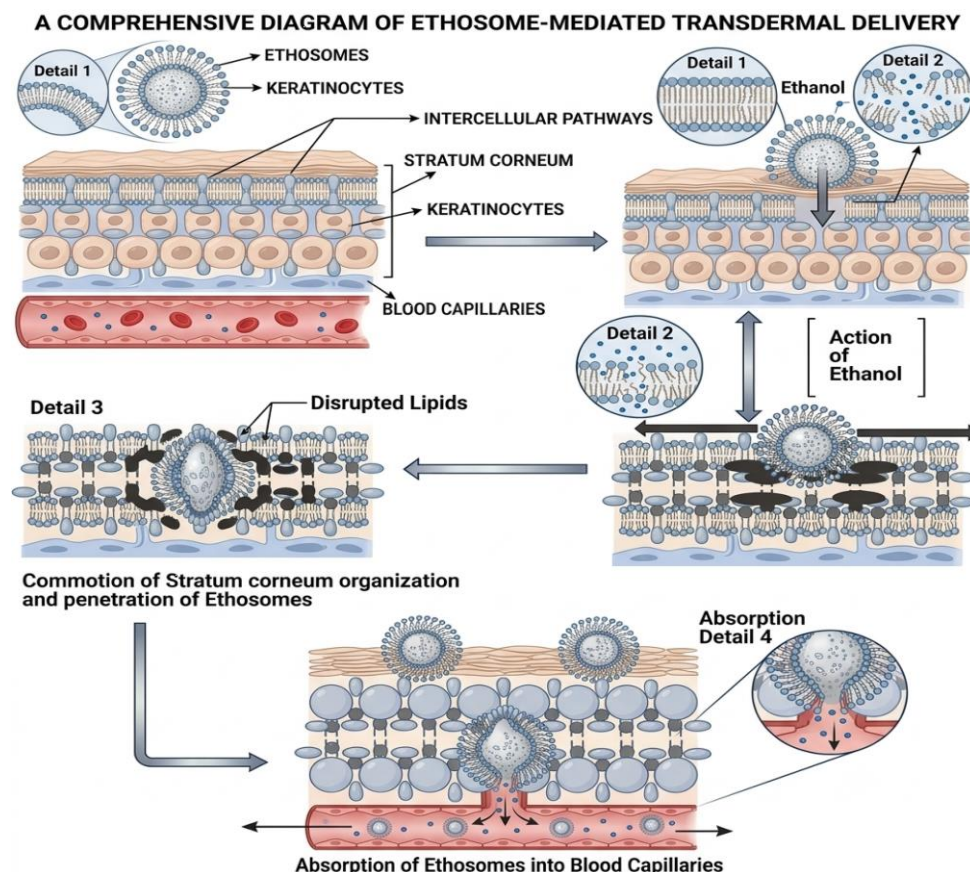
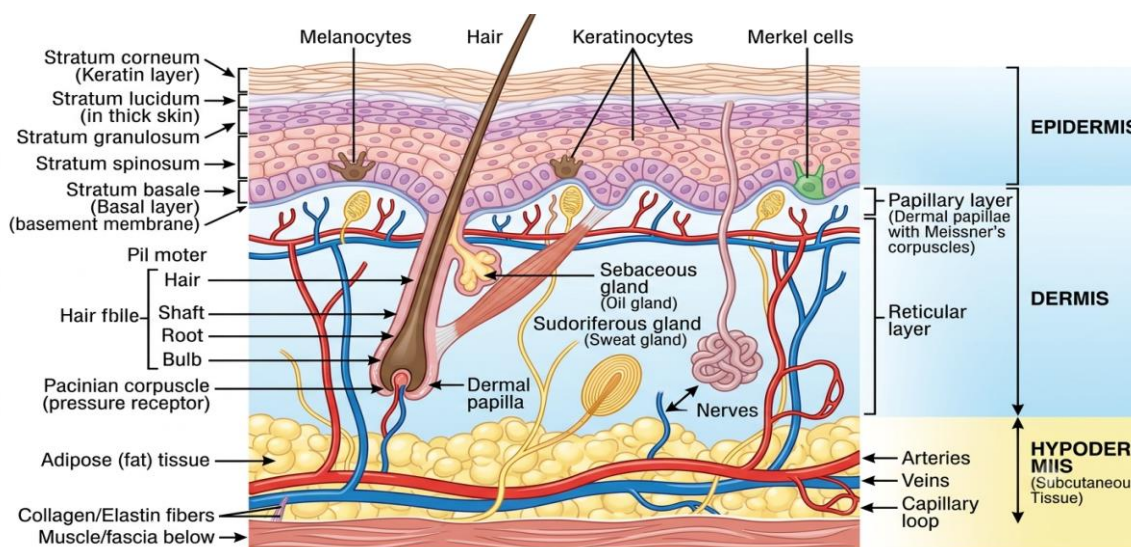


Fig. 2: MOA of Ethosome.**Skin Structure**

The epidermis, dermis, and hypodermis make up the skin's outermost layer. The primary cell type present in the human epidermis, keratinocytes, is the source of the 40–50 layers of stacked squamous epithelial cells that make up the epidermis. The stratum basale, stratum spinosum, stratum granulosum, and stratum corneum are the four layers that typically make up the epidermis. Progenitor cells, the youngest and most undifferentiated keratinocytes that constantly regenerate the epidermis, make up the deepest layer of the stratum basale. Human keratinocytes may take 30 to 40 days to move from the basal layer to the skin's surface during differentiation in order to undergo desquamation. Melanocytes, the cells responsible for producing pigment, and Merkel cells are also present in the basal layer. Keratinocytes contribute to keratin synthesis via differentiation when they divide vertically based on the basement membrane, and they aid in wound healing through proliferation when they divide horizontally. The basal lamina, a foundation membrane, divides this layer from the dermis. Nucleated keratinocytes make up the stratum granulosum and stratum spinosum. The stratum granulosum contains many granules that account for high amounts of keratin production, and these two strata cover around 15 to 20 layers. All layers of the epidermis include Langerhans

cells, albeit they are more common in the stratum spinosum. Keratin builds up and forms the stratum corneum as the nucleus and intracellular organelles progressively break down. As keratinisation advances, more keratin accumulates, creating a robust and flexible skin barrier made of dead keratinocytes. Topical delivery of molecules is greatly hampered by the stratum corneum, which normally generates a layer of keratinised keratinocytes that is 10–20 μm thick. The connective tissue made up of fibres like collagen and elastin makes up the majority of the dermal layer, which is situated underneath the epidermis. In contrast to the high quantity of keratinocytes needed in the epidermis, the fibroblasts that generate these fibres are few. Adipose tissues make up the hypodermis, which is located under the dermal layer. The tissues in this layer are generated from the mesoderm, much as in the dermis. As a result, fibroblasts may develop from mesenchymal stem cells found in the fat layer. Although they are mostly found in the dermis and hypodermis, blood vessels may sometimes reach the epidermis. For example, blood vessels are extensively dispersed across the epidermis in places with skin growths like warts, moles, or cancer. For transdermal distribution to be effective, the medicine must diffuse across all of these skin layers in addition to penetrating the stratum corneum.^[20]

**Fig. 3: Structure of skin.****Techniques for Ethosome Preparation**

New vesicular carriers called ethosomes have been developed for better transdermal medication delivery.

COLD METHOD

To produce ethosomes, this technique is often used. It was first presented by Touitou in 1996. Using this method, phospholipid, herbal drug extract, and other lipid materials were first dissolved in ethanol and vigorously stirred at room temperature in a covered vessel. Propylene glycol was then added at 40°C while the heat mix was being stirred up to 300°C, and water was

added at 300°C using a dropwise, streamline, or syringe pump. In order to get ethosomal suspension, the covered vessel was then agitated for five to thirty minutes at a speed of 700 to 2000 rpm using an overhead or magnetic stirrer. To get the necessary particle size, it was either sonified or extruded.^[21]

HOT TECHNIQUE

In this procedure phospholipid is heated at 30 degrees C in a water bath until a colloidal solution is achieved. Separately ethanol and propylene glycol are mixed and heated to 40 °C. Both combinations are then heated to

40°C and the organic and aqueous phases are added. The drug dissolves in either ethanol or water depending on whether it is hydrophobic or hydrophilic. The size of the ethosomal formulation vesicle can be reduced to the desired extent by extrusion method or probe sonication. Thus ethosomes are formed.^[22]

THIN-FILM HYDRATION TECHNIQUE

This methodology uses a novel strategy to extend the traditional liposome preparation procedure. A hydroethanolic solution is utilised to hydrate the lipid film rather than a strictly aqueous solution.^[23]

The process is as follows

- **Phospholipid Dissolution:** The phospholipid is first dissolved in chloroform. Chloroform may be utilised either by itself or in conjunction with methanol. Depending on the particular experiment, the ratios for the chloroform-methanol combination may be either 2:1 or 3:1. This is carried out in a dry, clean round-bottom flask.
- **Evaporation of Organic Solvents:** The mixture containing the phospholipid is evaporated by a rotating vacuum evaporator. This procedure removes the organic solvents (methanol and chloroform) at a temperature above the phase transition temperature of the lipid. This step ensures that all the remaining solvents are removed.
- **Removal of Solvent residues:** The lipid film was placed under vacuum for an entire night in order to remove any last residues of solvents. The total elimination of solvents is guaranteed by this prolonged vacuum time.
- **Hydration with Hydroethanolic Solution:** A solution made of ethanol and water is used to hydrate the lipid layer, which is now free of organic solvents. As an alternative, ethanol may be used with a phosphate-buffered saline (PBS) solution. The hydration procedure is carried out at a temperature appropriate for the characteristics of the particular phospholipid.
- **Rotating and Heating:** The lipid film undergoes both rotation and heating during hydration. The lipid coating in the hydroethanolic solution is more evenly distributed thanks to the rotation. The kind of phospholipid being utilised determines the temperature during this stage. For a certain amount of time, which may vary, the lipid layer is kept at this temperature. Depending on the needs of the experiment, the hydration period may be thirty minutes, an hour, or even six hours.^[23]

REVERSE PHASE EVAPORATION TECHNIQUE

This specialized process is composed of many independent processes and aims to produce large unilamellar vesicles:

- **Organic Phase Preparation:** The phospholipid is first dissolved in diethyl ether to prepare an organic phase. The phospholipid was dissolved in diethyl ether.

- **Emulsion Formation:** The organic and aqueous phases are mixed in an ultrasonic bath at a ratio of 3:1. This mixing leads to the formation of a water-in-oil emulsion. The ultrasonic bath helps in the emulsification process by enabling the ultrasonic vibrations to disperse the small water droplets within the organic solvent.

Cooling: During the ultrasonic mixing operation, the emulsion is kept at a low temperature of 0°C. Such cooling helps to stabilize the system and control the development of the emulsion.

- **Emulsion Stability:** Ultrasonication for 5 min at 0 °C improved the stability of the water-in-oil emulsion. It guarantees homogeneity of the water droplets distribution in the organic phase.
- **Solvent Removal:** The organic solvent (diethyl ether) is evaporated from the emulsion under low pressure after the stage of emulsification. In this operation the solvent is normally evaporated using a vacuum. When the solvent evaporates, the phospholipid forms a gel-like structure.
- **Gel to Colloidal Dispersion Transition:** The gel left after the removal of the organic solvent is gradually converted into a colloidal dispersion on application of strong mechanical agitation. This agitating action which disrupts the gel structure may produce vesicles in the aqueous phase. During the transition from gel to colloidal dispersion the phospholipid molecules most likely reorganize into bilayers to form vesicles.
- **Reverse-phase evaporation** is an uncommon technique for preparing large unilamellar vesicles. It is prepared by dissolving phospholipids in diethyl ether and ultrasonically agitating at 0°C for five minutes to obtain an organic phase mixed with an aqueous phase in a ratio of 3:1 v/v. This creates an emulsion of water and oil which is converted into a gel when the organic solvent is removed by low pressure. On vigorous stirring this gel becomes a colloidal dispersion.^[23]

TRANSMEMBRANE GRADIENT METHOD

The transmembrane pH-gradient approach uses pH variations between the basic exterior of the external phase and the acidic interior of the internal phase to "actively" load a medication into the ethosomal system. Water-soluble medications having protonizable amine functionalities may be used using this technique.^[23]

There are three steps in the process

1. Using an acidic buffer to create a blank ethosomal system,
2. Swirling the medication into the empty ethosomal suspension to actively load it; and
3. Adding a sodium hydroxide solution to create a pH gradient between the internal and exterior phases.

After that, the ethosomal system is incubated between 30 and 60 degrees Celsius, which enable the unionised medication to pass through the ethosomal vesicle bilayer

and get stuck. Before creating ethosomal systems with this technique, variables like as drug characteristics, phase pH, temperature, and incubation time must be taken into account. By using pH gradients between internal and exterior phases, this method offers a novel approach to actively load water-soluble medications into ethosomal vesicles, thereby improving drug encapsulation efficiency.^[23]

Various Herbal Extractions in Ethosomes as an API

Ethosomes are elastic, ultra-deformable nanovesicles made of water, phospholipids, and high ethanol concentrations (usually 20% to 45%). Ethosomes function as a "push and pull" carrier because the stratum corneum, the skin's outermost layer, often prevents complex, high-molecular-weight plant substances. While the ethanol makes the vesicles flexible enough to push deeply into tissues to provide specific comfort, it also fluidizes the skin's lipid barrier.^{[24],[25]}

Standard topical creams often don't work when utilising crude or standardised herbal extracts because the plant actives are too big, too hydrophilic, or too unstable. Ethosomes use two strategies to get around these obstacles:

- The Ethanol Effect: Ethanol interacts with the stratum corneum's densely packed lipid molecules, lowering their transition temperature and momentarily rupturing the skin barrier.^[26]
- Vesicle Deformability: The ethosome's lipid bilayer is very fluid due to the alcohol, which allows the small spheres to change shape and fit through the skin's enlarged intercellular gaps.^[27]
- Depot Effect: After passing through, they create "depot" in the skin's deeper layers, releasing the herbal chemicals gradually to relieve pain over time rather than in a short burst.

To give these prepared ethosomal suspensions the right viscosity and spreadability so that patients may apply them easily to sore joints or muscles, they are often combined with a hydrogel foundation (such as Carbopol 934).^[26]

By penetrating deeper muscle tissue, joints, and peripheral nerves, these herbal ethosomes methodically block pain rather than just numbing the skin's surface.

In order to use their active phytoconstituents for analgesic (pain-relieving) and anti-inflammatory activities, a number of herbal extracts are particularly packaged into ethosomal systems:

1) Five-leaved Chaste Tree (*Vitex negundo*)

- Plant Part & Extraction: Dried leaves, Cold maceration in hydroalcoholic solvent (ethanol/water).
- Active Biomarkers: Vitexin, casticin and certain particular volatile oils.
- Analgesic Mechanism Inhibits synthesis of main pro-inflammatory cytokines (TNF- alpha, IL- 6, IL-1

beta) downstream. Delivered deep into tissue via ethosomes it securely skips the skin surface to reach synovial fluids, preventing localised cartilage-destroying inflammatory signalling and reducing persistent arthritic pain.

- Design of Ethosome Formulation: Prepared by a cold synthesis method using 1% w/v Soya Lecithin and 40% v/v Ethanol, stably dispersed in a 1% Carbopol 934 hydrogel matrix to provide a sustained, prolonged drug delivery system.^[28]

2. Balloon vine (*Cardiospermum halicacabum*)

- Plant Part & Extraction: Aerial parts and leaves extracted with cold maceration in 85% methanolic or ethanolic solvent system.
- Active biomarkers: Flavonoid aglycones (Apigenin, Luteolin), phytosterols, certain polar saponins.^[25]
- Mechanism of analgesic: Selective control of nuclear factor kappa B pathway to suppress the production of LPS-induced COX-2, TNF-alpha and inducible nitric oxide synthase. It mimics the local non-steroidal anti-inflammatory effects, but without the gastrointestinal side consequences.^[26]
- Ethosome formulation profile: Vesicle sizes vary from 120 nm to 180 nm, which showed significant skin permeability metrics when formulated as a targeted roll-on or topical gel.

3. Bitter Ginger (*Zingiber zerumbet*)

- Plant Part & Extraction: Dried and crushed rhizomes were macerated in pure hexane or 100% ethanol to produce pure lipophilic fractions.
- Active ingredient: Zerumbone (a unique crystalline sesquiterpene)^[27]
- Analgesic Mechanism: Acts directly on peripheral sensory neurones to inhibit chemical nociceptive signalling. It inhibits nitric oxide generation in deep tissue matrices, hence dulling the pain pathways.
- Ethosome formulation profile: Prepared by cold method (1% w/v phosphatidylcholine, 40% v/v ethanol). It produces soft vesicular structures of very flexible nature in the range of 205.6 nm to 368.5 nm. This structure provides a 4-fold increase in the cutaneous penetration depth compared to a conventional raw extract.^[27]

4. Hog Plum (*Spondias pinnata*)

- Plant Part & Extraction: Coarse powder of mature stem bark extracted by continuous hot Soxhlet extraction with ethanol or methanol.
- Active Biomarkers: Gallic acid, Beta-sitosterol and specialised tannins.
- Analgesic Mechanism: Downregulates Myeloperoxidase enzyme activity and greatly reduces the overproduction of nitric oxide at the injury site. It decreases chemical hyperalgesia (oversensitivity to pain) by shielding local peripheral nerve roots from oxidative tissue damage.
- Ethosome formulation profile: Large lipophilic-heavy vesicular matrix structures (usually 190 nm to

260 nm) with significant negative surface charges (Zeta Potential of around -48mV) protecting the suspension against shelf life aggregation.^{[28],[29]}

5. Indian Beech (*Pongamia pinnata* / *Pongamia glabra*)

- Plant Part and Extraction: Mature seeds or dried leaves are extracted using either a hot Soxhlet or cold ethanol setup; leaf galls are extracted to separate unique furanoflavonoids.
- Active biomarkers: Karanjin, pongamol and furanoflavones.
- Analgesic Mechanism: Independently produces peripheral and central analgesic effects in a dose-related manner by inhibiting acute local mediators of pain. It decreases acute swelling from prostaglandins and persistent soft tissue pain with no systemic adverse effects.
- Formulation Profile of Ethosome: Customised vesicle design for optimal lipid membrane fluidisation to allow smooth passage of large/bulky furanoflavone structures across intercellular channels of the skin.^[30]

6. Lavender (*Lavandula angustifolia*)

- Plant Part & Extraction: Pure Lavender Essential Oil (LEO) is obtained from the fresh or dried blooming tops by steam distillation or hydrodistillation, which separates the inert plant fibres to get the volatile medicinal chemicals.
- Active Biomarkers The main active biomarkers responsible for the analgesic effectiveness of lavender essential oil are linalool (a monoterpene alcohol constituting 30–45%) and linalyl acetate (a monoterpene ester constituting 25–40%).
- Analgesic Mechanism : Lavender extract applied locally targets pain with interaction with peripheral opioid and cholinergic receptors to dull immediate nerve signalling. It also blocks voltage-gated sodium channels and calcium influx to slow acute pain transmission to the spinal cord. It also offers potent anti-inflammatory relief by inhibition of COX activity and suppression of nitric oxide and prostaglandin (PGE₂) synthesis, which helps immediately relieve tissue swelling and localised throbbing.
- Ethosomal Formulation Profile: Ultra tiny nanoscale ethosomes (110-160 nm) of Soya Phosphatidylcholine (1.0-3.0% w/v), ethanol (30-40% v/v) and filtered water were used to overcome the volatility and hydrophobic character of lavender oil and to load it. The system successfully encapsulates its major lipophilic actives, linalool and linalyl acetate, in the phospholipid bilayer at high entrapment efficiency of 75–88% and maintains physical stability by a substantial negative surface charge (-33 mV to -45 mV) preventing vesicle aggregation. Finally, this liquid ethosomal suspension is blended with 1% Carbopol gel base to generate a non-greasy topical gel formulation that is

optimised for deep penetration into the skin and localised comfort over painful muscles or joints.^{[31],[32],[33]}

7. Rosemary (*Rosmarinus officinalis*)

Plant Parts & Extraction: Therapeutic products from rosemary (*Rosmarinus officinalis*) are mainly derived from its leaves and flowering tops using two main extraction methods based on the desired profile: steam distillation, which isolates a volatile, monoterpene-rich essential oil fraction, and solvent extraction (hydroalcoholic or organic solvents), which extracts a dense, polyphenol-rich fraction containing heavy phenolic compounds and flavonoids.^[34]

Active Biomarkers: The pharmacologically active components of rosemary are divided into two main biochemical categories: volatile terpenoids (mainly found in the essential oil) represented by biomarkers such as 1,8-cineole (eucalyptol), α -pinene, camphor and the anti-inflammatory sesquiterpene β -caryophyllene, and non-volatile phenolics (concentrated by solvent extraction), which are made up of strong phenolic diterpenes, predominantly carnosic acid and carnosol, and the hydroxycinnamic acid derivative rosmarinic acid.

Analgesic Mechanism of Action: Rosemary reduces pain through a multi-target mechanism: carnosol and rosmarinic acid inhibit COX-1/COX-2 enzymes to prevent pro-inflammatory prostaglandin synthesis, 1,8-cineole and β -caryophyllene regulate TRP channels and CB₂ receptors to desensitise peripheral pain nerves, and rosmarinic acid neutralises reactive oxygen species to protect tissues and nerves from oxidative damage.^{[35],[36]}

Ethosomal Formulation Profile: Rosemary extracts are put into ethosomes (100–150 nm), which are nanoscale, highly deformable lipid vesicles made up of phospholipids and 20–45% ethanol to bypass the skin's lipid barrier. Ethanol increases skin permeability by fluidizing the intercellular lipid layers and providing flexibility to the vesicles to press into the deeper layers of the dermis. These ethosomes have a persistent negative surface charge (-10 to -45 mV) that prevents aggregation and show >80% entrapment efficacy for both hydrophilic rosmarinic acid and lipophilic carnosic acid, giving continuous localised pain alleviation.^[37]

8. Peppermint (*Mentha × piperita*)

- Plant Parts & Extraction: Peppermint therapeutic formulations are obtained from the fresh or partly dried leaves and flowering tops of the plant, using two main methods depending on the target profile: steam distillation, which applies precise heat to separate volatile, lipophilic monoterpenes for pure essential oil, and solvent extraction (via hydroalcoholic mixtures), which extracts heavy, non-volatile compounds in an effort to obtain a polyphenol and flavonoid dense fraction.^[38]
- Active Biomarkers: The main active biomarkers in peppermint are divided into two main classes:

volatile monoterpenes (primarily (-)-menthol at 30–50% of the essential oil mass, along with menthone, isomenthone and 1,8-cineole) and non-volatile phenolics (concentrated by solvent extraction, including rosmarinic acid, luteolin and eriocitrin).

- Analgesic Mechanism of Action: Peppermint's ability to provide targeted pain relief is a multi-mechanism effect: menthol selectively activates TRPM8 channels to create a localised cooling effect that masks pain signals sent to the spinal cord, while also blocking voltage-gated sodium and calcium channels in sensory nerves to provide a local anaesthetic effect. Moreover, peppermint works as a muscle relaxant limiting calcium influx via L-type channels to cure cramps and spasms, while also reducing major pro-inflammatory cytokines, including IL-1 β , IL-6 and TNF- α to diminish localised tissue inflammation.^[39]
- Ethosomal Formulation Profile: Raw peppermint extracts are encapsulated in ethosomes—nanoscale lipid vesicles (100–160 nm) consisting of phospholipids and 20–45% ethanol—to overcome the skin's barrier and avoid fast evaporation. The high ethanol concentration functions as a penetration enhancer by fluidizing skin lipids while making the vesicles ultra-deformable to push deep into dermal layers to deliver lipophilic menthol and hydrophilic phenolics. The ethosomes have a steady negative surface charge (-15 to -40 mV) preventing clumping, and excellent entrapment effectiveness. This provides a sustained-release depot at the location of muscle or nerve discomfort.^[40]

9. Turmeric (*Curcuma longa*)

- Turmeric (*Curcuma longa*) therapeutic preparations are made from the underground rhizomes of the plant. Two main processing methods are used depending on the extract of choice. Organic solvent extraction (ethanol, acetone or ethyl acetate) produces a concentrated crystalline powder that contains a higher fraction of lipophilic polyphenols. Supercritical CO₂ extraction allows a clean separation of both volatile essential oils and lipophilic pigments without toxic residues.
- Active Biomarkers: Turmeric bioactivity is associated with two major chemical families: (a) curcuminoids, the non-volatile lipophilic polyphenols led by curcumin (diferuloylmethane, accounting for 75–80% of the fraction), demethoxycurcumin and bisdemethoxycurcumin and (b) volatile terpenoids present in the essential oil matrix comprising key sesquiterpenes such as alpha-turmerone, beta-turmerone and ar-turmerone.^[41]
- Analgesic Mechanism of Action: Turmeric works on pain by blocking Nuclear Factor-kappa B at the transcriptional level, so stopping the generation of pro-inflammatory cytokines including IL-1 β , IL-6, and TNF- α . It inhibits the activity of the enzymes COX-2 and iNOS to prevent the formation of the prostaglandin E-2 (PGE-2) to reduce

inflammatory pressure on pain receptors. It also downregulates peripheral TRPV1 heat/pain channels and its phenolic structure scavenges reactive oxygen species (ROS) and prevents oxidative nerve irritation.^[42]

- Ethosomal Formulation Profile: To overcome the extreme hydrophobicity and low skin penetration of raw curcumin, it is entrapped inside ethosomes, which are ultra-deformable lipid vesicles (110–170 nm) made up of phospholipids and 20–45% ethanol. The high ethanol concentration fluidizes the lipid barrier of the skin and softens the vesicle walls, enabling these extremely elastic carriers to push deep into the epidermal and dermal layers. This ethosomal system has a significantly negative surface charge (-20 to -45 mV) preventing aggregation and with an entrapment efficacy of over 85%, therefore shielding the curcumin from degradation and generating a prolonged release depot at the sites of inflammation or joint pain.^[43]

10. Capsaicin (*Capsicum annuum*, *Capsicum frutescens*)

- Plant Parts & Extraction Type: Capsaicin is a strong alkaloid found in the ripe fruits of chilli peppers (*Capsicum* species) and is extracted by solvent extraction, in which dried peppers are treated with organic solvents such as ethanol or ethyl acetate to obtain a concentrated “capsicum oleoresin” that is rich in capsaicinoids, lipophilic pigments, and volatile compounds. This crude oleoresin is chromatographically purified and vacuum distilled to generate pharmaceutical-grade active ingredients, isolating the pure capsaicin crystals from the surrounding fatty acids.
- Active Biomarkers: Capsaicin (primary biomarker), Dihydrocapsaicin, Nordihydrocapsaicin, Homocapsaicin, Homodihydrocapsaicin.^[44]
- Analgesic Mechanism of Action: Capsaicin provides sustained pain relief by selectively binding to TRPV1 receptors on C and A delta nerve fibres, opening ion channels to allow an influx of calcium and sodium that creates an initial burning sensation and depletes localised pain neuropeptides such as Substance P. The chronic calcium excess with extended exposure disturbs the cellular architecture of the nerve terminal, momentarily defunctionalizes and prunes the epidermal nerve terminals. Unable to send signals to the central nervous system and stripped of Substance P, these neurones enter a condition of long-lasting desensitisation until they ultimately regenerate.^[45]
- Ethosomal Formulation Profile: Encapsulating raw capsaicin into ethosomes—nanovesicles (90–175 nm) made of phospholipids and high quantities of ethanol (20–45% v/v)—overcomes topical burning and poor skin penetration. The high alcohol content fluidizes the skin's lipid barrier and makes the vesicle membranes ultra-flexible enabling them to push deep into dermal layers to distribute capsaicin

and dihydrocapsaicin. Supported by a strong negative surface charge (-30 to -55 mV) that inhibits clumping, this approach delivers 80–85% entrapment efficiency, minimises surface irritation and creates a sustained release depot for deep anti-inflammatory and pain relief.^[46]

11. *Zingiber officinale* Roscoe

- Plant Part & Extract Type: Ginger extract is obtained from the subterranean rhizome of *Zingiber officinale* Roscoe. The main product obtained is ginger oleoresin, which is obtained by extraction with non-polar organic solvents. The result is a concentrated mixture of volatile terpenes and non-volatile pungent chemicals.
- Active Biomarkers: [6]-Gingerol, [6]-Shogaol, alpha-Zingiberene, ar-Curcumene, beta-Sesquiphellandrene.^[47]
- Analgesic Mechanisms: Ginger decreases pain and inflammation by inhibiting COX-2 and LOX pathways to decrease PGE-2 and leukotrienes and downregulating NF-kappaB translocation to prevent the generation of pro-inflammatory cytokines such as TNF-alpha, IL-1beta, and IL-6. Also its components are structurally similar to capsaicin and desensitise TRPV1 sensory receptors and inhibit voltage gated Na⁺ channels blocking action potentials and release of pain signalling neurotransmitters such as Substance P.^[48]
- Ethosomal Formulation Profile: Nanometric vesicles (100–200 nm) composed of phospholipids, high-concentration ethanol (20–45%), and a hydroethanolic core enable ethosomes to circumvent the skin's outer barrier and low oral availability. The high ethanol concentration makes the skin lipid layers and the vesicle membranes fluid, with enough flexibility to press deep into skin tissues. The significant negative charge on the surface (~-30 mV) precludes aggregation for reliable distribution. When applied, they are characterised by a biphasic release profile: an initial burst release of surface-bound active chemicals followed by continuous non-Fickian diffusion over a 24-hour period, offering targeted and long-lasting pain relief.^[49]

12. *Eucalyptus globulus* Labill. or *Eucalyptus citriodora* Hook

- Plant Part & Extract Type: Eucalyptus essential oil is prepared by steam distillation or hydrodistillation of fresh or partly dried leaves of *Eucalyptus globulus* Labill. or *Eucalyptus citriodora* Hook. (Family: Myrtaceae). The technique provides a very volatile, lipophilic oil rich in active monoterpenes for medicinal purposes.
- Active Biomarkers: 1,8-Cineole (Eucalyptol), Citronellal, alpha-Pinene, Limonene, p-Cymene
- Analgesic Mechanisms: The major biomarker of eucalyptus oil, 1,8-cineole, has an analgesic effect by being a selective agonist of TRPM8 receptors, producing a cooling sensory signal to counter-irritate

and mask peripheral pain pathways. Simultaneously, it inhibits cyclooxygenase (COX) pathways and directly reduces arachidonic acid metabolism to limit the formation of Prostaglandin E2 and Leukotriene B4, thereby decreasing peripheral nociceptor sensitisation.^[50] It also has anti-oxidant properties.^[51]

- Ethosomal Formulation Profile: Encapsulation of extremely volatile eucalyptus oil into ethosomal nanovesicles (110–180 nm) prepared with soybean phosphatidylcholine (1–4%) and high ethanol concentrations (20–40%) avoids fast evaporation and overcomes poor skin penetration. The ethanol transiently fluidizes the stratum corneum lipid barrier enabling the elastic, extremely stable vesicles (zeta potential -25 to -35 mV) to deliver active terpenes deep into skin tissue layers. This delivery mechanism results in a regulated release profile, with an initial burst release for immediate cooling pain relief, and a gradual diffusion over 24 hours.^[52]

13. Nutmeg (*Myristica fragrans*)

- Plant Part & Extract Profile: Nutmeg and mace are two different spices obtained from the same fruit structure of *Myristica fragrans*, a tropical evergreen tree native to the Moluccas. Nutmeg is the inner dried seed kernel while mace is the lacy scarlet aril around it. This plant is processed by steam distillation to obtain volatile essential oils, by solvent extraction to obtain dense oleoresins containing volatile and heavy lipid fractions or by fluid extraction with supercritical CO₂, the pharmaceutical gold standard for the extraction of heat sensitive bioactives, without the residual chemical solvents.
- Key Active Biomarkers: The pharmacological activity of *Myristica fragrans* is attributed to a complex of diverse secondary metabolites: volatile phenylpropanoids (myristicin, elemicin and safrole) that impart central nervous system and analgesic effects; monoterpenes (sabinene, alpha-pinene, beta-pinene and limonene) that confer antioxidant benefits and improve skin penetration; and non-volatile neolignans and phenolics (macelignan, licarin A and eugenol) present in the oleoresin that impart potent anti-inflammatory and antimicrobial activity.^[53]
- Analgesic & Anti-Inflammatory Mechanism: Nutmeg reduces pain and inflammation via peripheral pathways wherein its active neolignans (such as macelignan) and eugenol downregulate COX-2 expression to inhibit prostaglandin (PGE-2) synthesis, and at the same time lower circulating levels of Substance P to interrupt pain signal transmission and soothe local tissue swelling.^[54]
- Ethosomal Profile: The optimised nutmeg ethosomal system possesses a nano-sized vesicle profile (100–250 nm) for maximum skin penetration, high entrapment efficiency (75–85%) of its lipophilic bioactives, and a high negative surface charge (-15

to -35 mV) for preventing vesicle aggregation through electrostatic repulsion, which achieved thermodynamic stability and high dermal absorption.^[55]

14. Wintergreen Oil (Gaultheria fragrantissima/Gaultheria procumbens)

- Plant Part & Extraction: Wintergreen essential oil is extracted from the fermented leaves of *Gaultheria procumbens* (Family: Ericaceae) by steam or hydrodistillation (0.5-1.5% oil). Before distillation, the leaves are treated with enzymes to hydrolyse the glycoside gaultherin to methyl salicylate, so that the resultant oil is essentially pure active ingredient.^[56]
- Active Biomarkers: Wintergreen oil contains mostly methyl salicylate (95–99%) as the main bioactive constituent responsible for its primary analgesic and anti-inflammatory actions. This primary molecule is accompanied by its natural precursor, gaultherin, its active tissue metabolite, salicylic acid, and secondary flavonoids and terpenoids, which add to the antioxidant and therapeutic value.
- Analgesic Mechanism: Topically applied methyl salicylate passes through the skin tissues and is hydrolysed to salicylic acid which directly inhibits COX-1 and COX-2 enzymes to stop the creation of prostaglandins and reduce inflammation. At the same time, it works as a counter-irritant, generating a sense of warmth that relieves musculoskeletal discomfort and also induces modest vasodilation, improving local blood flow and reducing muscular stiffness.^[57]
- Ethosomal profile: The prepared ethosomes commonly show vesicle size in the range of 100–300 nm, polydispersity index <0.3, zeta potential values around ± 30 mV, and entrapment effectiveness >80%. Wintergreen oil-loaded ethosomes showed enhanced skin permeation, sustained drug release, improved bioavailability, reduced local irritation and prolonged analgesic and anti-inflammatory effects compared to conventional topical formulations. Hence, wintergreen oil-loaded ethosomes are a promising nanocarrier system for topical treatment of musculoskeletal disorders.^{[58],[59]}

CONCLUSIONS

The combination of herbal medicines with modern nanocarriers like ethosomes is a major advancement in topical and transcutaneous medication delivery. Traditional herbal extracts are generally limited by poor solubility, high molecular size and low skin permeability. Ethosomal gels are able to bypass these barriers. The combination of ethanol and phospholipids liquefies the lipids of the stratum corneum, resulting in significantly improved penetration of complex phytoconstituents.

Extensive literature further shows that herbal ethosomal gels are found to be superior to conventional topical formulations like standard creams, macrogol gels etc. in aspect of entrapment efficiency, skin retention and

therapeutic efficacy in various disorders such as inflammation, microbial infections, alopecia, hyperpigmentation and others. Moreover, the gel basis offers the needed viscosity, longer contact duration and easy administration essential for patient compliance.

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