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ADVANCES IN HERBAL AND SYNTHETIC TRANSFEROSOMES: ROUTES, FORMULATION CHALLENGES AND COMPARATIVE PERFORMANCE

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ABSTRACT
Background: Transferosomes are ultra-deformable vesicular carriers widely investigated for enhancing drug delivery across biological barriers. Both herbal and synthetic transferosomes have gained attention for improving permeability, bioavailability, and therapeutic efficacy. However, a comparative understanding of their formulation strategies, therapeutic performance, and associated challenges remains limited. **Methodology:** A systematic literature review was conducted to compare herbal and synthetic transferosomes. A total of 100 research and review articles were analyzed, including 50 studies each on herbal and synthetic formulations. Data were categorized based on formulation benefits, challenges, routes of administration, and dosage forms, and analyzed to determine the frequency of these parameters. **Results and Discussion:** Synthetic transferosomes exhibited higher permeability (30%), stability (18%), solubility (10%), and vesicle deformability (13%) due to their defined composition and controlled formulation. However, scalability 27%, vesicle size control, and encapsulation efficiency remained major challenges. Herbal transferosomes demonstrated improved bioavailability (20%) and drug delivery efficiency (18%), likely due to the synergistic effects of phytoconstituents. Nevertheless, they showed greater extract variability (28%) and formulation instability (18%). Transdermal delivery was the predominant route, accounting for 80% of herbal and 65% of synthetic formulations, with gels being the most common dosage form. **Conclusion:** Synthetic transferosomes provide better formulation control and reproducibility, whereas herbal systems offer enhanced therapeutic potential. Optimization of formulation parameters and stability is essential to improve the translational applicability of both systems.

INTRODUCTION

Herbal medicine refers to therapeutic remedies derived from natural plant sources and has been used for healthcare since ancient times [1]. Early civilizations in China, Greece, India, Italy (representing Rome) and the Middle East relied extensively on medicinal plants for disease prevention and treatment, forming the basis of structured traditional systems such as Ayurveda, Siddha, Unani and Traditional Chinese Medicine (TCM) [2,3]. According to the World Health Organization (WHO), nearly 80% of the global population continues to

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depend on traditional plant-based medicines for primary health care needs [4]. The increasing global preference for natural therapies, coupled with their perceived safety & cultural acceptance, has driven sustained research efforts toward improving the quality, safety, and efficacy of herbal formulations [5].

Phytopharmaceuticals are standardized pharmaceutical preparations derived from plant-based bioactive constituents rather than synthetic chemicals [6]. These preparations, obtained from roots, leaves, bark, seeds, berries, and flowers [7], contain diverse phytoconstituents such as alkaloids, flavonoids, tannins, polyphenols, lignans, terpenoids, quinones, and coumarins that exhibit broad pharmacological activities. Herbal medicines offer advantages including multi-target therapeutic action, potential synergistic effects, cultural acceptance, and comparatively fewer severe adverse effects, which contribute to their sustained global use [1–4]. However, despite their therapeutic potential, many phytoconstituents exhibit poor bioavailability due to large molecular size, hydrophilic nature, chemical instability & limited membrane permeability [8,9].

Additionally, variability in phytochemical composition arising from geographical, seasonal, and processing factors, along with challenges in standardization and regulatory control, may restrict their consistent therapeutic performance, particularly in systemic and transdermal delivery. In contrast, synthetic drugs produced through controlled chemical synthesis form the backbone of modern pharmaceutical therapy for acute and chronic diseases. They offer distinct advantages such as high purity, well-defined chemical structure, precise mechanism of action, standardized dosing, reproducible pharmacokinetics, rapid onset of action, and strong therapeutic efficacy. Extensive clinical evaluation and regulatory validation further support their reliability and widespread use. Nevertheless, synthetic drugs may be associated with adverse effects, toxicity, potential drug resistance in certain classes, higher research and development costs, and occasional issues related to long-term safety and patient compliance, thereby encouraging ongoing exploration of optimized and safer drug delivery alternatives [10]. Topical and transdermal drug delivery systems (TDDS) have emerged as effective approaches to enhance drug bioavailability and patient compliance. Conventional topical dosage forms such as ointments, creams, gels, pastes, and lotions enable localized drug delivery with reduced systemic exposure [11]. Transdermal systems further provide controlled release, avoidance of first-pass metabolism, and improved therapeutic outcomes. However, the stratum corneum acts as a formidable barrier, permitting the passage of small, lipophilic molecules while significantly restricting hydrophilic and high-molecular-weight compounds, including many phytoconstituents [12]. To overcome these limitations, substantial research has focused on novel drug delivery systems (NDDS) designed to enhance stability, permeability, and therapeutic efficacy. Among these, vesicular carriers such as liposomes, phytosomes, niosomes, ethosomes, and transferosomes have shown considerable promise [13]. These systems improve drug solubility, protect labile constituents, enhance skin penetration, and provide sustained release, making them particularly suitable for both herbal and synthetic drugs [14]. Transferosomes, in particular, have gained significant attention for topical and transdermal applications. They are ultra-deformable lipid vesicles composed of phospholipids and edge activators (surfactants) that confer elasticity and enable passage through narrow intercellular spaces of the stratum corneum [15]. By mimicking biological membranes and deforming under osmotic gradients, transferosomes enhance drug permeation across intact skin barriers. This property is especially advantageous for herbal phytoconstituents with inherently poor membrane permeability. The formation of transferosome drug complexes can improve lipid solubility, skin affinity, drug deposition, and sustained release profiles [16].

The global expansion of the transdermal drug delivery market further underscores the growing importance of advanced vesicular technologies. The TDDS market has been estimated at approximately USD 83.67 billion in 2025. It is projected to grow substantially over the next decade, reflecting increasing demand for non-invasive, controlled-release, and patient-friendly drug delivery strategies. Transferosomes represent an emerging and innovative sub-segment within this expanding domain, with growing interest in both synthetic and herbal formulations [17]. This review aims to systematically compare herbal and synthetic transferosome formulations by evaluating their formulation approaches, therapeutic performance, commonly used routes of administration, and dosage forms. It also examines key performance parameters such as permeability, bioavailability, stability, and drug delivery efficiency, along with major formulation challenges including extract variability, encapsulation efficiency, and scalability to understand their potential for improved drug delivery and clinical translation.

TRANSFEROSOMES

Transferosomes, introduced by Gregor Cevc in 1991, derive their name from the Latin transferre (to carry across) and Greek soma (body), meaning a "carrying body" for barrier transport [16,18]. They are ultra-deformable vesicles composed of an aqueous core surrounded by a flexible lipid bilayer containing phospholipids and edge activators. Although structurally similar to liposomes, transferosomes exhibit superior elasticity and membrane adaptability, enabling them to pass through narrow intercellular spaces of the stratum corneum. Their ability to retain moisture and maintain hydration enhances vesicle stability and promotes efficient transdermal drug delivery compared to conventional liposomes [19]. Transferosomes offer advantages such as improved pharmacokinetics, site-specific targeting, enhanced skin penetration, sustained drug release, reduced dose requirement, minimized systemic side effects, and improved patient compliance through non-invasive routes [20–22]. However, they also have limitations including physical and chemical instability, drug leakage during storage, complex and costly manufacturing processes, limited drug loading for certain molecules, and challenges in large-scale production.

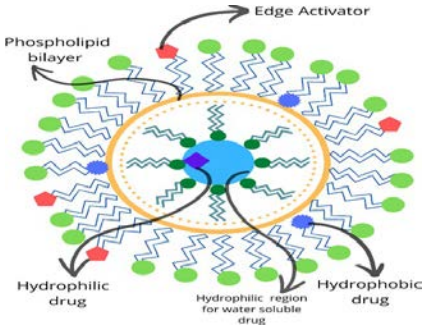

Figure 1: Structure of Transferosomes [23]

COMPOSITION OF TRANSFEROSOMES

- **Phospholipids (Vesicle-forming agents):** Phospholipids are the primary structural components that form the lipid bilayer of transferosomes. In an aqueous environment, they self-assemble into bilayer vesicles with a hydrophilic head and hydrophobic tail arrangement. This structure allows encapsulation of hydrophilic drugs in the aqueous core and lipophilic drugs within the lipid bilayer. Phospholipids also contribute to biocompatibility and biodegradability. Examples: Soya phosphatidylcholine (SPC), Egg phosphatidylcholine (EPC), Dipalmitoyl phosphatidylcholine (DPPC), Hydrogenated phosphatidylcholine [24].
- **Edge Activators (Surfactants):** Edge activators are single-chain surfactants added to destabilize the lipid bilayer slightly, increasing its fluidity and elasticity. They reduce interfacial tension and impart ultra-deformability, enabling transferosomes to pass through skin pores much smaller than their own size without rupture. The concentration of edge activator directly influences vesicle flexibility and permeability. Examples: Sodium cholate, Sodium deoxycholate, Tween 20, Tween 80, Span 60, Span 80 [24].
- **Aqueous Phase (Hydration Medium):** The aqueous phase is used during vesicle formation and constitutes the internal core of the transferosome. It dissolves hydrophilic drugs and maintains vesicle stability. Buffer systems are often used to maintain suitable pH. Examples: Purified water, Phosphate buffer (pH 6.4–7.4) [24].
- **Active Pharmaceutical Ingredient (Drug):** The drug may be hydrophilic, lipophilic, or amphiphilic. Hydrophilic drugs are entrapped in the aqueous core, whereas lipophilic drugs are incorporated into the lipid bilayer. Examples: Diclofenac (lipophilic), Insulin (hydrophilic), Curcumin (lipophilic phytoconstituent), and Ketoconazole (antifungal) [24].
- **Optional Additives (Stabilizers/Enhancers):** Additional components may be included to enhance stability, rigidity, or permeability. Cholesterol improves membrane stability and reduces leakage, while antioxidants prevent lipid oxidation. Small amounts of ethanol may enhance penetration in certain formulations. Examples: Cholesterol, Butylated hydroxytoluene (BHT), and Ethanol [24].

Together, these components provide structural integrity, ultra-deformability, enhanced skin penetration, and efficient drug delivery in transferosomal formulations [25].

ROUTES OF ADMINISTRATION / MECHANISM OF TRANSFEROSOMES

Administration through Skin

As shown in Figure 2, Transferosomes are ultra-deformable vesicles composed of phospholipids and edge activators that penetrate deep skin layers due to their elasticity and response to transdermal osmotic gradients [26]. Under non-occlusive conditions, they deliver approximately 0.1 mg lipid/hour/cm², exceeding conventional systems [27,28]. Their movement is driven by the water gradient between the hydrated viable epidermis (~75%) and dry stratum corneum (~15%), enabling intact skin penetration without rupture. During passage, they deform reversibly while maintaining integrity and may interact with skin lipids through fusion or endocytosis-like mechanisms [29].

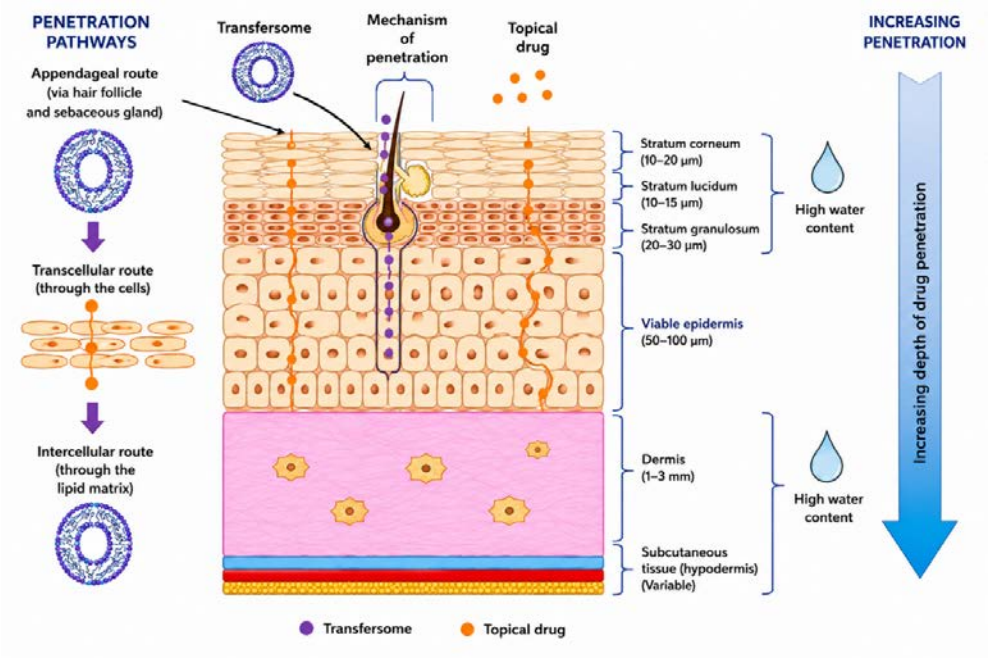

Figure 2: Mechanism of Transferosomes through skin [30]

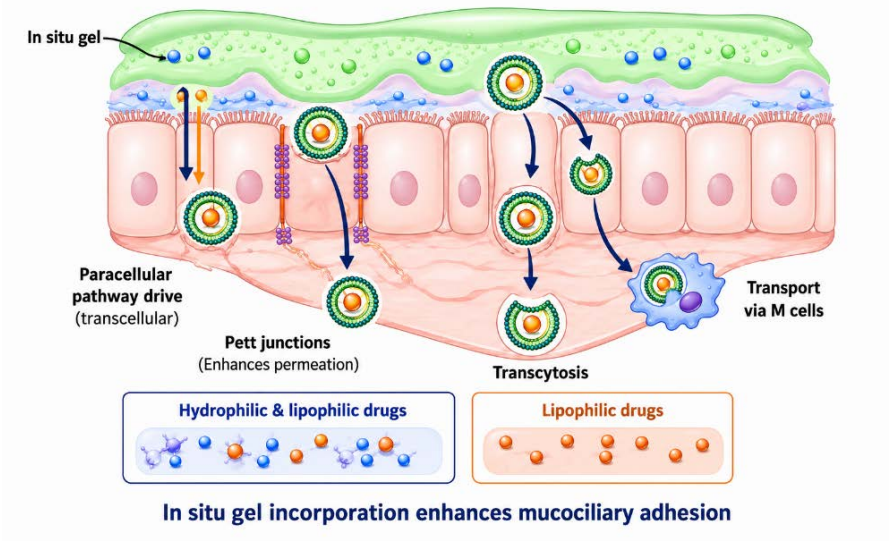

Figure 3: Mechanism of transferosomes through the nasal route

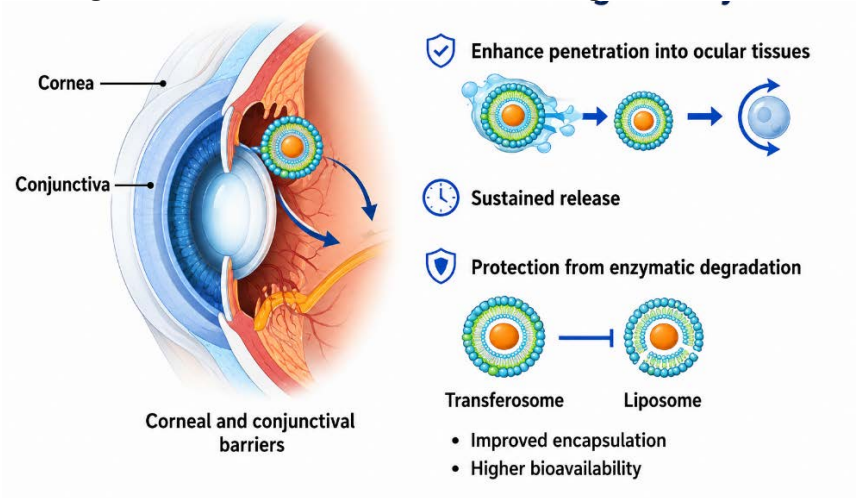

Figure 4: Mechanism of transferosomes through the ocular route

Administration through Nasal Route

Transferosomes cross the nasal epithelium via paracellular, transcellular, and transcytotic pathways due to their high flexibility. As shown in Figure 3, they transiently modulate tight junctions, enhance membrane fluidity, and increase residence time through bioadhesion, improving absorption of hydrophilic and lipophilic drugs, including peptides and proteins. Incorporation into in situ gels further enhances mucoadhesion and sustained release [31].

Administration through Ocular Route

Due to their deformability, transferosomes pass through corneal and conjunctival barriers without rupture. They enhance penetration into ocular tissues, provide sustained release, and protect drugs from enzymatic degradation. Compared to liposomes, they offer improved encapsulation efficiency and bioavailability for non-invasive ocular delivery [32].

Administration through Oral Route

Transferosomes protect drugs from gastric acidity and enzymatic degradation and facilitate intestinal absorption via tight junction modulation, endocytosis, or transcytosis. Their elasticity may enhance systemic bioavailability and sustain release. However, stability issues and manufacturing challenges limit large-scale clinical application [33,34].

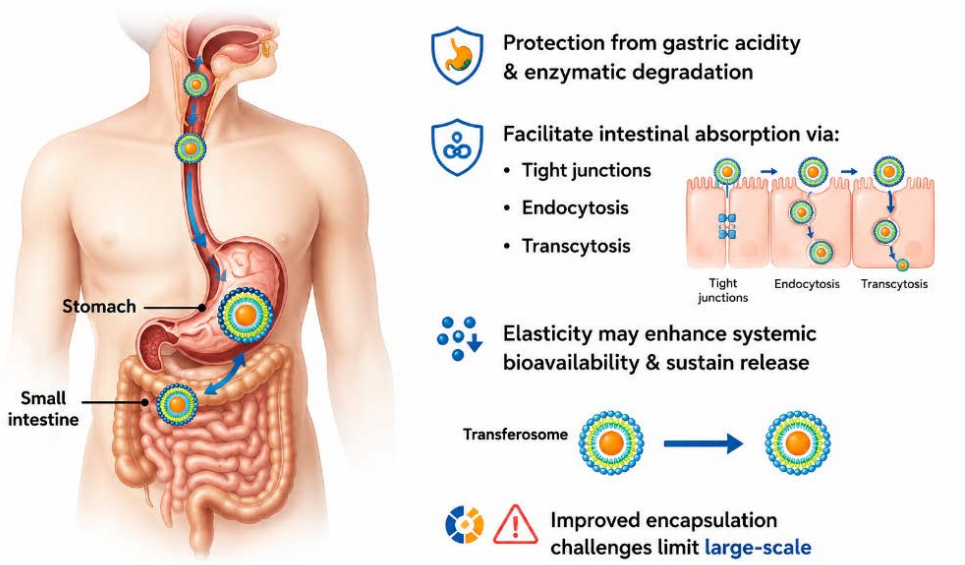

Figure 5: Mechanism of Transferosomes through Oral Route

WHY ARE TRANSFEROSOMES BETTER THAN OTHER CARRIERS?

Transferosomes possess significant advantages over other vesicular carriers such as liposomes, ethosomes, niosomes, and electrosomes due to their ultra-deformable structure and superior penetration mechanism.

- Liposomes are phospholipid bilayer vesicles capable of encapsulating hydrophilic and lipophilic drugs, improving bioavailability and reducing systemic toxicity. However, their rigid structure limits penetration mainly to the stratum corneum and upper epidermis. They are also prone to oxidation, hydrolysis, drug leakage, and high production costs, restricting their efficiency in transdermal delivery [35,36].
- Ethosomes contain high ethanol concentrations that disrupt stratum corneum lipids and enhance skin permeation compared to conventional liposomes. Nevertheless, they exhibit lower elasticity than transferosomes, may cause skin irritation or dryness, and face stability issues due to ethanol volatility, with drug deposition largely limited to superficial and mid-skin layers [37].
- Niosomes are vesicles formed from non-ionic surfactants and cholesterol, offering better chemical stability and cost-effectiveness than liposomes. However, they may undergo aggregation, fusion, drug leakage, and their lower elasticity limits deep skin penetration compared to transferosomes [23].
- Electrosomes are vesicles prepared using electroporation to enhance membrane permeability & facilitate delivery of large biomolecules. Despite this advantage, they remain underexplored & face challenges such as instability, complex and costly preparation, and limited application in transdermal delivery [38].

Table 1: Comparison of Transferosomes and other Carriers

Feature	Transferosomes	Liposomes	Ethosomes	Niosomes	Electrosomes
Vesicle composition	Phospholipids + edge activators (surfactants)	Phospholipid bilayers	Phospholipids + high ethanol content	Non-ionic surfactants + cholesterol	Electroporated vesicles
Deformability/ Elasticity	Ultra-deformable, highly elastic	Rigid, less deformable	Less elastic than transferosomes	Less elastic, prone to aggregation	Variable, often unstable
Skin penetration	Deep penetration through intact stratum corneum via osmotic gradient	Limited to surface/upper skin layers	Moderate penetration by lipid disruption	Poor to moderate penetration	Potentially good but less studied
Drug encapsulation	High entrapment efficiency for hydrophilic and lipophilic drugs	Moderate, prone to leakage	Moderate to high depending on ethanol	Moderate, vesicle fusion and leakage issues	Suitable for large biomolecules
Stability	Good stability with controlled formulation	Prone to oxidation, hydrolysis, leakage	Moderate, ethanol volatility affects shelf life	Good chemical stability but aggregation risk	Less stable, preparation complexity
Toxicity / Irritation	Low toxicity, biocompatible phospholipids	Generally safe	Possible irritation due to ethanol	Generally safe	Safety profile under study
Ease of Preparation	Requires optimized formulation and surfactant types	Established but costlier	Simple but careful ethanol handling needed	Easy and economical but requires optimization	Complex setup and costly
Applications	Ideal for transdermal and topical delivery, including large molecules and herbal actives	Surface drug delivery and some systemic	Topical and some systemic delivery	Topical controlled release	Limited to advanced targeted drug delivery
Key Advantage	Combines ultra-flexibility with osmotic-driven deep skin penetration	Biocompatible but poor skin penetration	Enhances penetration via ethanol	Stable, cost-effective alternative	Potential for controlled delivery of complex drugs

FACTORS AFFECTING TRANSFEROSOMES

To achieve an optimized transferosome formulation, it is essential to regulate several process parameters that influence the properties of transferosomes.

- **Effect of Phospholipid:** Edge Activator Ratio: The phospholipid-to-surfactant ratio is a critical factor influencing transferosomal performance, including vesicle size, entrapment efficiency, deformability, and skin permeation. Increasing the concentration of edge activators enhances membrane fluidity and reduces vesicle size, thereby improving deformability and permeation. However, excessive surfactant levels may create pores in the lipid bilayer, resulting in drug leakage and reduced encapsulation efficiency. In contrast, insufficient surfactant concentrations produce larger and less flexible vesicles with lower permeation capacity. Therefore, an optimized ratio is essential to maintain a balance between vesicle stability and elasticity [39]. Supporting this, F. Mayangsari et al. reported that an 85:15 phospholipid-to-surfactant ratio provided optimal entrapment efficiency and deformability in berberine-loaded transferosomes [40]. However, the effectiveness of this ratio depends on the physicochemical characteristics of the incorporated drug. For hydrophilic drugs such as Metformin HCl, the 85:15 ratio improved deformability. It produced a 15-fold increase in permeation [60], whereas lipophilic compounds such as Curcumin demonstrated entrapment efficiency approaching 99% [49], likely due to stronger incorporation into the phospholipid bilayer. Additionally, ionic surfactants may enhance permeation but increase instability, while non-ionic surfactants generally provide better stability and biocompatibility.
- **Effect of Solvents:** Commonly used solvents in transferosome formulation include methanol and ethanol,

selected based on the solubility and compatibility of formulation components. Proper solvent selection ensures complete dissolution and formation of a clear solution, which is essential for stable thin film formation and efficient vesicle assembly after hydration [41].

Ethanol also acts as a penetration enhancer; Williams and Barry reported increased flux of drugs such as hydrocortisone, 5-fluorouracil, estradiol, and levonorgestrel across rat skin due to improved drug partitioning and stratum corneum permeation [42]. However, high ethanol concentrations may increase bilayer permeability, leading to drug leakage and reduced entrapment efficiency. Similarly, Zheng et al. noted that incomplete solubilization disrupts lecithin assembly, resulting in poor vesicle formation and low encapsulation, emphasizing the importance of optimal solvent selection for stable and efficient transferosome formulations [43].

- **Effect of different edge activators:** The chemical structure and concentration of surfactants significantly influence the deformability, vesicle size and entrapment efficiency of transferosomes. An increase in HLB value, carbon chain length, hydrophilicity of the head group and surfactant concentration generally reduces vesicle size by enhancing membrane fluidity. Common edge activators such as Tween 80, Span 80, sodium deoxycholate and sodium cholate decrease vesicle size up to an optimal concentration (around 15%); beyond this level, micelle formation may occur, limiting vesicle stability and size reduction.

  N. Dudhipala et al. reported that edge activator concentration, lipid content, and hydration medium pH significantly affect entrapment efficiency and elasticity of transferosomal formulations [44]. Additionally, C. K. Kim et al. identified sodium cholate as a suitable edge activator for ultradeformable liposomes in transdermal plasmid DNA delivery due to its low cellular toxicity [45].
- **Effect of Hydrating Medium:** Water or saline phosphate buffer are two options for the hydrating medium with pH 6.5-7. The medium's pH must be adjusted to balance formulation properties, biological compatibility, and administration route.

  Transfersomes, resembling cell membrane phospholipids, allow only unionized drugs to pass and bind to the bilayer; thus, maintaining the drug's unionized form with the correct hydration pH enhances its penetration and encapsulation [46].

BENEFITS & CHALLENGES OF TRANSFEROSOMES

- **Benefits:** Transferosomes offer superior skin penetration due to their ultra-deformable and elastic bilayer structure, enabling them to cross intact biological barriers efficiently. They enhance drug bioavailability, improve entrapment of hydrophilic and lipophilic drugs, and provide sustained and controlled release. Their ability to deliver drugs through non-invasive routes such as transdermal and topical pathways improves patient compliance and reduces systemic side effects. Additionally, transferosomes enable site-specific targeting, dose reduction, and enhanced therapeutic efficacy compared to conventional vesicular systems [47].

- **Challenges:** Despite these advantages, transferosomes face limitations including physical and chemical instability, phospholipid oxidation, drug leakage during storage, and sensitivity to pH and temperature variations. High surfactant concentrations may reduce entrapment efficiency, while large-scale manufacturing remains complex and costly. Issues related to long-term stability, scalability, and regulatory approval also restrict their widespread commercial application [47].

BENEFITS & CHALLENGES OF HERBAL TRANSFEROSOMES

Herbal transferosomes integrate phytoconstituents with ultra-deformable vesicles to enhance skin permeation, bioavailability, and stability of poorly soluble compounds such as flavonoids and alkaloids. They provide improved entrapment, sustained release, dose reduction, and better patient compliance through non-invasive delivery. However, challenges include variability of plant extracts, difficulty in standardization, vesicle instability, possible phytochemical–lipid interactions, oxidative degradation, high production cost, scalability issues, limited clinical evidence, and regulatory constraints [48].

Some of the benefits and challenges of herbal transferosomes faced by researchers were discussed:

In a study by Sharma P et al., herbal transferosomes were reported as effective elastic vesicles capable of enhancing transdermal delivery of poorly permeable phytoconstituents such as curcumin. Incorporating edge activators improved bilayer flexibility, enabling better skin penetration, targeted delivery, and enhanced bioavailability. The optimized formulation showed superior wound-healing activity compared

to conventional ointments, as evidenced by increased tensile strength and hydroxyproline content. However, the study also highlighted key challenges, including the inherent low permeability and poor absorption of herbal extracts and relatively low entrapment efficiency (3.51%), emphasizing formulation limitations [28].

Barbalho et al. developed transferosomes as a novel platform to enhance ocular delivery of curcumin, a poorly soluble BCS class IV drug with anti-inflammatory potential. The ultra-deformable vesicles improved corneal and conjunctival penetration via transpore hydrotaxis, showed high entrapment efficiency (>99%), narrow particle size (<150 nm), sustained triphasic release and good biocompatibility without ocular irritation. Curcumin loading further stabilized the vesicles. However, challenges included curcumin's poor solubility and pH instability, strict limitations on ocular excipients, complex corneal barriers, rapid precorneal drainage and possible systemic loss through conjunctival absorption, highlighting formulation and delivery constraints [49].

Balasubramanyam P et al. developed curcumin-loaded transferosomes to overcome its poor oral bioavailability, low aqueous solubility, high first-pass metabolism and limited skin permeability. Conventional topical forms show inadequate penetration due to the stratum corneum barrier, and the formulation required careful optimization of lecithin–surfactant ratio and solvent system. The optimized transferosomal formulation (PC: Span 80, 85:15) demonstrated high entrapment efficiency (89.6%), enhanced 24-h permeation (50.61% vs. 33.51% for conventional gel), prolonged release, improved stability and scalability. The study concluded that elastic vesicles significantly enhance transdermal delivery of curcumin compared to traditional formulations [50].

Mayangsari et al. investigated a transferosomal emulgel to improve the delivery of berberine chloride (BBR), a drug with <1% oral bioavailability due to P-glycoprotein efflux, extensive intestinal metabolism, and gastrointestinal side effects at high doses. Its hydrophilic nature and quaternary ammonium structure further limit skin permeation, with conventional gels largely remaining on the surface. The optimized transferosomal formulation (F2) enhanced skin penetration 3.8-fold compared to the non-transferosomal emulgel and achieved high entrapment efficiency (93.97%). The emulgel was homogeneous, greaseless, easily spreadable, and stable for at least three months, demonstrating improved transdermal delivery and formulation stability [40].

Nangare et al. developed a freeze-dried *Mulberry* leaf extract–based transferosomal gel for acne vulgaris, a multifactorial disorder affecting nearly 85% of individuals. The formulation utilized natural antioxidants such as quercetin, offering improved safety and reduced toxicity compared to synthetic agents. Ultra-deformable transfersomes enhanced skin penetration and provided prolonged release, while low-cost mulberry leaves offered economic benefits. However, challenges included the complex pathogenesis of acne, skin penetration barriers, and the need for precise optimization of phospholipid–surfactant ratios to prevent micelle formation or vesicle aggregation. The transferosomal gel also protected the extract from degradation, unlike the conventional control gel, which showed reduced antioxidant activity & drug content [51].

Sahu et al. investigated a nanotransferosome gel containing methanolic extract of *Solanum xanthocarpum* for psoriasis management. Psoriasis presents major challenges due to the strong barrier function of the stratum corneum, multifactorial autoimmune pathology, and limitations of existing therapies, which are often ineffective and associated with adverse effects. Natural extracts further suffer from poor permeability and low bioavailability, requiring stable and patient-friendly delivery systems. The optimized nanotransferosomes (146.3 nm) significantly enhanced skin permeation (82.86% vs. 35.28% for conventional gel) and improved epidermal & dermal retention. The formulation exhibited notable anti-psoriatic, anti-inflammatory & antioxidant activity, along with good stability over 3 months, indicating its potential as an effective topical therapy [52].

Wongrakpanich et al. evaluated *Phyllanthus emblica* extract–loaded transferosomes for hair growth promotion. The aqueous extract, at non-toxic levels, stimulated growth factors (VEGF, IGF-1, HGF) comparable to 1% minoxidil, while transfersomes enhanced follicular delivery beyond conventional solutions. The formulation remained stable for three months at 4°C and 30°C, and the extract showed strong antioxidant potential due to vitamin C and phenolics such as gallic acid. However, higher antioxidant ethanolic extracts showed increased cytotoxicity, and storage at 40°C caused vesicle instability. Encapsulation efficiency was lower for hydrophilic gallic acid (46.4%) than lipophilic ellagic acid (97.8%), and phytochemical variability

posed standardization challenges. Overall, PE-loaded transferosomes were considered a promising approach for hair loss management [53].

Abdallah et al. developed quercetin-loaded transferosomes to enhance topical wound healing. Quercetin's poor solubility and limited skin penetration required a nano-vesicular formulation, with optimization achieved through factorial design to balance entrapment efficiency and particle size. Extensive characterization (e.g., DSC, TEM) confirmed vesicle integrity and drug incorporation. The optimized formula (F6) achieved 4.3-fold higher skin deposition than drug suspension and 1.89-fold higher than liposomes. In vivo studies showed improved re-epithelialization and collagen maturation with no irritation observed. The study demonstrated that transferosomes can effectively improve the stability, penetration, and therapeutic efficacy of herbal compounds in wound management [54].

Pandey and Sharma formulated a transferosome-based *Centella asiatica* gel to improve wound healing. Conventional herbal forms show poor solubility and low skin penetration, limiting efficacy. The optimized formulation (F3) demonstrated higher wound contraction (92.3% by Day 14), two-fold greater flux and sustained release (76.5%/24 h) compared to conventional ointments. Histology confirmed improved collagen formation and re-epithelialization. However, vesicle stability required precise phospholipid–cholesterol optimization, and limited prior in vivo data indicated the need for further studies [39].

Benedetto et al. developed a transferosome-based formulation of optimized black tea extract to prevent UVB-induced skin damage. Using a Box–Behnken design, they enhanced polyphenol extraction, achieving a higher theaflavin yield (~11%) than conventional methods. The nano-sized transferosomes (~60 nm) were stable for five months and improved cellular uptake (1.8–3-fold). In vitro studies showed protection against UVB-induced cell death, restoration of collagen, and reduction of inflammatory markers (IL-6, COX-2, iNOS). However, challenges included complex extraction optimization, overcoming the stratum corneum barrier, safety concerns with existing UV filters, and the need for in vivo and clinical validation [55].

Table 2: Herbal Transferosomes: Benefits and Challenges

Herbal Drug/Extract	Key Benefits	Major Challenges	Comparative Performance
Curcumin [28]	Improved transdermal delivery; enhanced bioavailability; superior wound healing; increased tensile strength & hydroxyproline	Low inherent permeability; poor absorption; low entrapment efficiency (3.51%)	Better wound healing and tissue repair than synthetic systems
Curcumin (ocular) [49]	High entrapment (>99%); improved corneal penetration; sustained release; non-irritant	Poor solubility; pH instability; precorneal drainage; excipient limitations	Better ocular compatibility and lower irritation
Curcumin [50]	High EE (89.6%); enhanced 24-h permeation; prolonged release; scalable	Poor solubility; first-pass metabolism; optimization of lecithin–surfactant ratio	Comparable sustained release to synthetic formulations
Berberine chloride [40]	3.8-fold higher permeation; high EE (93.97%); stable emulgel	<1% oral bioavailability; hydrophilicity limiting skin permeation	Improved dermal delivery by bypassing first-pass metabolism
Mulberry leaf extract [51]	Improved penetration; prolonged release; protected antioxidants; cost-effective	Acne complexity; vesicle aggregation; ratio optimization issues	Lower toxicity than synthetic anti-acne drugs
S. xanthocarpum extract [52]	Enhanced permeation (82.86%); better skin retention; anti-psoriatic activity	Strong stratum corneum barrier; low herbal bioavailability	Better anti-psoriatic activity and retention
P. emblica extract [53]	Enhanced follicular delivery; antioxidant activity; growth factor stimulation	Cytotoxicity at high doses; vesicle instability at 40°C; variable EE	Better antioxidant and follicular targeting
Quercetin [54]	4.3-fold higher skin deposition; improved wound healing; non-irritant	Poor solubility; need for factorial optimization	Improved wound healing with low irritation
C. asiatica [39]	Higher wound contraction (92.3%); sustained release; improved collagen formation	Vesicle stability concerns; limited prior in vivo data	Superior collagen synthesis and wound repair
Black tea extract [55]	Stable nano-vesicles (~60 nm); enhanced uptake; UVB protection	Complex extraction; skin barrier limitation; need for clinical validation	Better antioxidant and photoprotective activity

As shown in Table 2, a considerable difference in encapsulation efficiency (EE) was observed among curcumin-loaded transferosomal formulations, with reported values ranging from as low as 3.51% to as high as 99%. This variation suggests that formulation design plays a major role in determining the amount of curcumin successfully entrapped within the vesicles. Lower EE values were generally associated with insufficient optimization of formulation variables, which may have reduced the vesicles' ability to retain the drug. In contrast, studies reporting higher EE values utilized carefully optimized phospholipid and edge activator ratios, suitable solvent systems & appropriate surfactants that improved vesicle formation & drug incorporation. Since curcumin is highly lipophilic, its entrapment is strongly influenced by the composition and characteristics of the lipid bilayer. Therefore, factors such as lipid concentration, surfactant selection, solvent system, and preparation method collectively contribute to the observed differences in encapsulation efficiency. These findings indicate that successful curcumin loading depends largely on proper formulation optimization rather than on the physicochemical properties of the drug alone.

BENEFITS AND CHALLENGES OF SYNTHETIC TRANSFEROSOMES

Synthetic transferosomes enhance transdermal delivery through ultra-deformable lipid vesicles, improving skin penetration, bioavailability, entrapment efficiency, and sustained drug release. Their defined composition ensures reproducibility, scalability, and easier regulatory control. However, limitations include possible skin irritation from surfactants, phospholipid oxidation, high production cost, formulation complexity, stability concerns, and challenges in large-scale manufacturing and regulatory approval [47].

Some of the benefits and challenges of Synthetic transferosomes faced by researchers were discussed:

Shaji and Lal developed a transferosomal gel of piroxicam to enhance transdermal delivery for inflammatory conditions such as rheumatoid arthritis. The ultradeformable vesicles produced a three-fold increase in permeation compared to conventional gels, enabled sustained release, reduced gastrointestinal side effects, and showed superior anti-inflammatory activity. However, formulation faced challenges including the stratum corneum barrier, instability with certain phospholipids (e.g., Phospholipon 90H), sensitivity to sonication and hydration temperature, lipid oxidation, and limited drug-loading capacity, all requiring careful optimization to maintain stability and efficacy [56].

Nayak et al. (2026) studied the development and evaluation of a diclofenac-loaded transferosomal gel aimed at improving transdermal drug delivery for the management of musculoskeletal pain. The research focused on formulating ultradeformable vesicles using suitable phospholipid and edge activator combinations, followed by characterization of vesicle size, entrapment efficiency, and stability. The optimized formulation demonstrated significantly enhanced skin permeation and sustained drug release over 24 hours compared to conventional formulations. In vitro and in vivo evaluations confirmed improved anti-inflammatory and antioxidant activity with reduced systemic side effects, indicating that transferosomal systems can effectively enhance the therapeutic performance and bioavailability of diclofenac while offering a safer and more efficient alternative to traditional delivery methods [57].

Singh A et al. developed felodipine-loaded transferosomes to overcome its low oral bioavailability (15–20%) due to extensive first-pass metabolism. The optimized transfersomal gel showed markedly higher relative bioavailability (358.42%), 256% enhanced permeation over the control gel, and sustained plasma levels with reduced fluctuations, improving patient compliance. However, formulation was challenging due to the stratum corneum barrier, limitations of earlier systems (e.g., SLNs, high-lag-time patches), and the need for precise optimization of vortexing/sonication time, drug loading (<1% w/w), and lipid–surfactant ratio to avoid micelle formation or membrane damage. Stability issues such as vesicle aggregation during storage further emphasized the complexity of developing effective transdermal nanovesicles [58].

Balata et al. developed ivabradine HCl-loaded transferosomes to enhance transdermal delivery and overcome its low oral bioavailability (≈40%) due to first-pass metabolism. The optimized transfersomal film achieved a 2.4-fold increase in bioavailability (AUC), prolonged Tmax (6 h vs. 2 h), and extended half-life, enabling once-daily dosing with no skin irritation. However, challenges included overcoming the stratum corneum barrier, optimizing surfactant and phospholipid ratios, preventing drug leakage (e.g., with Tween 80), controlling

vesicle size with ionic surfactants, and confirming drug encapsulation through DSC and TEM. The study demonstrated improved systemic delivery and sustained therapeutic action via a transdermal approach [59].

Mazhar et al. developed a metformin HCl-loaded transferosomal gel with eucalyptus oil to overcome its low permeability (BCS class III), short half-life, frequent dosing, gastrointestinal side effects, and first-pass metabolism associated with oral therapy. Conventional transdermal systems also present cost and stability issues. The optimized transfersomal gel showed a 15-fold increase in drug flux over plain gel, sustained plasma levels up to 24 h, and significantly higher Cmax and AUC compared to oral solution. The formulation was non-irritant, skin-compatible, and suitable for scale-up via thin-film hydration, demonstrating improved bioavailability and therapeutic potential [60].

Bhujbal et al. developed tonabersat-loaded transferosomes to improve ocular delivery for the treatment of dry eye disease. The ultra-deformable vesicles enhanced drug penetration into the cornea, conjunctiva, and deeper ocular tissues, achieved more than 80% entrapment efficiency, prolonged ocular residence time through the formation of a phospholipid-based bionic tear film, and enabled targeted anti-inflammatory therapy. However, several formulation challenges were identified, including the poor aqueous solubility of tonabersat and physiological ocular barriers such as tight junctions and reflex tearing, which limited drug retention and absorption. Significant instability was also observed at temperatures ≥25°C, resulting in drug leakage, crystal formation, phospholipid hydrolysis, vesicle aggregation, and a decline in pH. Factors such as surfactant concentration, lipid composition, and elevated temperature significantly affected vesicle integrity and stability, thereby requiring refrigerated storage at approximately 5°C or below to maintain formulation stability [37].

Zheng et al. developed itraconazole-loaded transferosomes to improve antifungal therapy. The ultradeformable vesicles enhanced skin penetration, enabled stable plasma levels via transdermal delivery, reduced hepatotoxicity linked to systemic therapy, improved patient compliance, and showed no skin irritation. However, the formulation posed challenges: itraconazole's high lipophilicity required ethanol–chloroform for solubilization; excess soybean lecithin increased particle size and flocculation; inappropriate bile salt ratios risked micelle formation; and high-pressure homogenization could cause vesicle damage and drug leakage. Stability was also temperature- and pH-sensitive, as heat accelerated lipid hydrolysis. After optimization, the formulation achieved ~80% entrapment efficiency and acceptable stability [43]. In her study, Najma Easa emphasizes that non-invasive insulin delivery can improve adherence and reduce pain associated with daily injections. Buccal and pulmonary routes bypass hepatic first-pass metabolism & enhance patient comfort. Transfersomes facilitate mucosal transport through their ultra-deformable structure, while lyophilized buccal patches improve insulin stability & minimize leakage. However, insulin's high molecular weight (5.8 kDa), hydrophilicity, and enzymatic degradation limit permeability. Formulation challenges include balancing cholesterol for entrapment versus flexibility, heat-induced denaturation during sonication, reduced osmotic driving force in hydrated TR146 cell models, variable saliva affecting absorption, and decreased mucoadhesion due to cryoprotectants like sorbitol [23].

As shown in Table 3, although synthetic transferosomes generally exhibit better formulation consistency & reproducibility than herbal systems, they are not free from stability-related challenges. Several studies reported temperature.-dependent vesicle aggregation, phospholipid hydrolysis, drug leakage, and changes in vesicle size during storage, particularly under elevated temp. conditions. The phospholipid bilayer of transferosomes is susceptible to oxidative degradation and hydrolytic reactions, which can compromise membrane integrity and reduce drug retention over time. Furthermore, inappropriate concentrations of edge activators may increase membrane fluidity beyond the optimal level, leading to vesicle fusion, aggregation, or leakage of the encapsulated drug. Synthetic transferosomes may also undergo physicochemical instability during long-term storage due to interactions between lipids, surfactants, and encapsulated drugs. Consequently, despite the use of chemically defined active pharmaceutical ingredients, stability remains a significant formulation challenge, explaining why synthetic transferosomes exhibit stability-related issues at rates comparable to those observed in herbal transferosomal systems.

Methodology

A systematic literature review was conducted to comparatively analyze herbal and synthetic transferosomes in terms of their benefits, challenges, routes of administration, and dosage forms reported in the literature. A total of 100 research and review

articles were collected from scientific databases, including PubMed, Scopus, Google Scholar, and ScienceDirect, using relevant keywords such as transferosomes, herbal transferosomes, synthetic transferosomes, and vesicular drug delivery systems. The study selection and screening process was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines to ensure transparency, systematic identification, and reproducibility of the literature selection process. The detailed workflow of article identification, screening, eligibility assessment, and final inclusion is presented in Figure 6.

Table 3: Synthetic Transferosomes: Benefits and Challenges

Drug	Key Benefits	Major Challenges	Comparative Performance
Piroxicam [56]	3-fold higher permeation; sustained release; reduced GI effects; superior anti-inflammatory activity	Stratum corneum barrier; phospholipid instability; lipid oxidation; limited drug loading	Better reproducibility and anti-inflammatory control
Diclofenac acid [57]	Improved Antioxidant and Anti-inflammatory; reduced musculoskeletal inflammation	Low permeability; aggregation; drug leakage; storage instability	Faster anti-inflammatory response
Felodipine [58]	84.5% EE; 88.5% higher permeation; sustained plasma levels	SC barrier; strict lipid–surfactant optimization; vesicle aggregation	Better systemic cardiovascular delivery
Ivabradine HCl [59]	2.4-fold ↑ bioavailability; prolonged Tmax; once-daily dosing	Drug leakage; surfactant ratio limits; vesicle size control	Superior dose control and bioavailability
Metformin HCl [60]	15-fold ↑ flux; 24-h sustained levels; higher Cmax & AUC; non-irritant	Low permeability (BCS III); formulation complexity	Better systemic delivery for diabetes management
Tonabersat (ocular) [37]	>80% EE; enhanced ocular penetration; prolonged residence	Poor solubility; ocular barriers; instability ≥25°C	Better targeted ocular delivery
Itraconazole [43]	~80% EE; enhanced penetration; reduced hepatotoxicity	Solubility issues; vesicle flocculation; heat-induced instability	More reliable antifungal delivery
Insulin [23]	Improved adherence; bypass first-pass; enhanced mucosal transport	High MW; enzymatic degradation; mucoadhesion and stability issues	Better peptide drug delivery

Comparative Analysis of Benefits and Challenges in Herbal and Synthetic Transferosomes

A comparative review of herbal and synthetic transferosomal formulations was conducted using the PRISMA approach. Based on the PRISMA flow chart, a total of 100 research articles were selected for detailed analysis, including 50 articles related to herbal transferosomes and 50 articles related to synthetic transferosomes. The selected studies were carefully screened according to predefined inclusion & exclusion criteria to ensure the relevance and quality of the literature included in the review.

An equal sampling strategy consisting of 50 herbal and 50 synthetic transferosome studies was adopted to facilitate a balanced comparative analysis between both formulation categories and to minimize overrepresentation of the comparatively larger synthetic transferosome literature. Original research articles were primarily used to extract formulation data, experimental outcomes, and comparative quantitative analyses. Review articles were utilized only for background information, mechanistic explanations, and general theoretical discussion related to transferosomal drug delivery systems. To avoid data duplication and "double-counting," experimental findings discussed in review articles were cross-verified with the corresponding original research publications, and unique datasets and primary experimental observations were included in the final analysis.

Each article was systematically evaluated to extract data related to the formulation, characterization & evaluation of transferosomes. Particular emphasis was placed on identifying the reported benefits and challenges associated with both herbal & synthetic transferosomes. The collected information included formulation parameters, vesicle characteristics, drug loading capacity, permeation efficiency, bioavailability enhancement, therapeutic efficacy, stability, and safety profiles. A balanced comparative analysis was performed to assess the advantages of both systems, including enhanced drug permeation, improved bioavailability, targeted drug delivery, increased therapeutic effectiveness, and reduced side effects. In addition, commonly reported limitations & formulation challenges were systematically documented. These included issues related to formulation instability, variability in herbal extracts, reproducibility concerns, vesicle size control, encapsulation efficiency, scalability, storage stability & regulatory constraints. Furthermore, formulation-related observations and experimental outcomes reported across the selected studies were critically

compared to identify similarities, differences, and emerging trends between herbal and synthetic transferosomal approaches. A limitation statement discussing the possible influence of the equal sampling strategy on the representation of the available literature has also been included in the discussion section to ensure transparency and methodological clarity.

Literature Search and Selection of Herbal and Synthetic Transferosome Studies

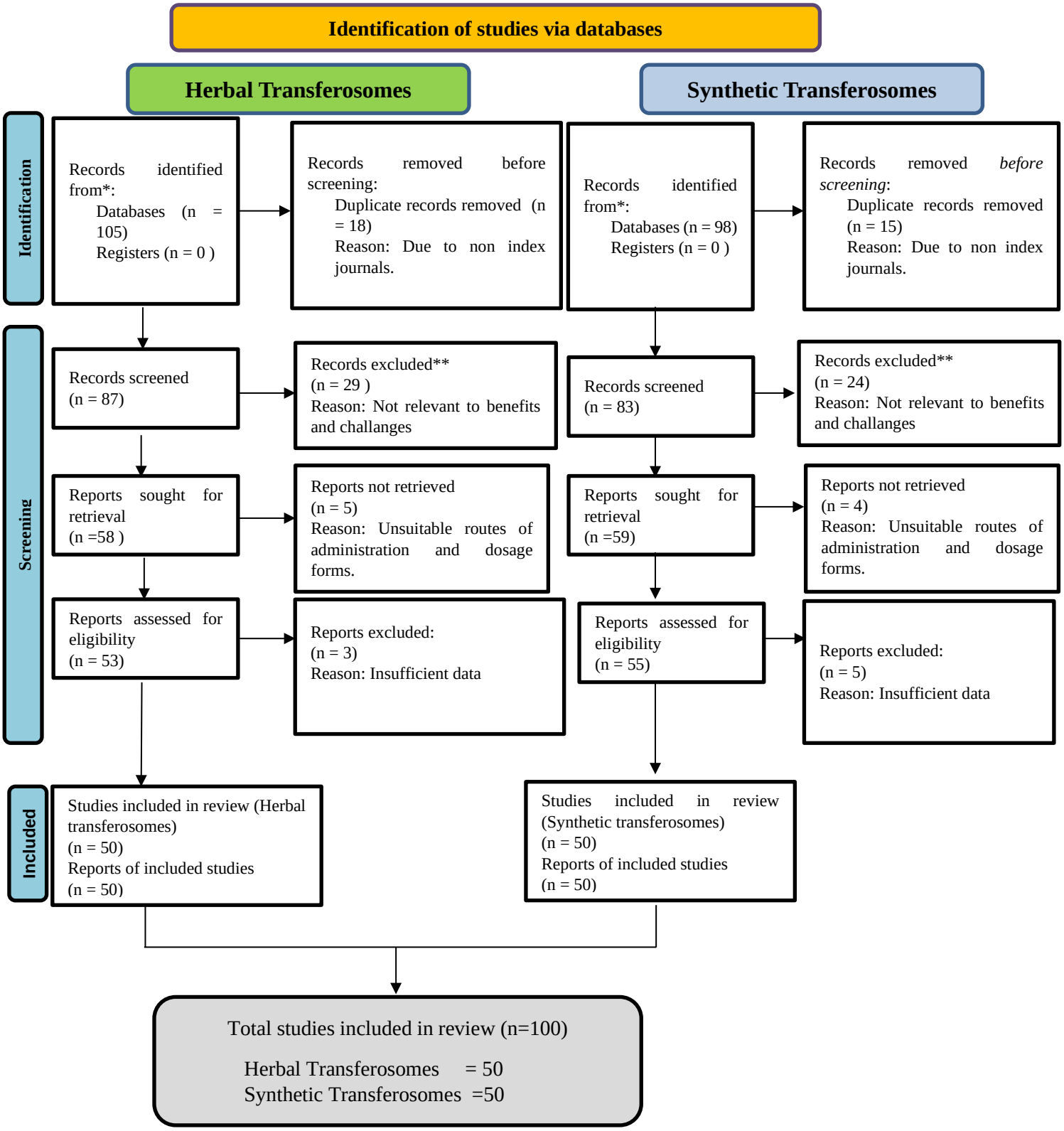

Figure 6: PRISMA flow diagram showing the literature search and selection process for herbal and synthetic transferosome studies.

Analysis of routes of administration and dosage forms in herbal and synthetic transferosomes

Furthermore, the literature was also analyzed to determine the commonly reported routes of administration (such as transdermal, nasal, ocular, and oral) and dosage forms (including gels, creams, patches, and ointments) used for herbal and synthetic transferosome formulations. The extracted data were systematically categorized into benefits, challenges, routes of administration, and dosage forms. Finally, the comparative findings were quantitatively analyzed and visually represented using bar graphs to clearly illustrate the frequency and distribution of these parameters for both herbal and synthetic transferosomes reported in the literature.

RESULTS AND DISCUSSION

Comparison of benefits and challenges of herbal & synthetic transferosomes

As shown in Table 4 and Figure 7, both herbal and synthetic transferosomes demonstrated various benefits and formulation-related challenges. Among synthetic transferosomal studies, enhanced permeability was the most commonly reported advantage, observed in 30% of the studies (15/50 articles). Improved stability was reported in 18% (9/50 articles), vesicle deformability in 13% (6/50 articles), and solubility enhancement in 10% (5/50 articles). These percentages represent the frequency with which studies report improvement in the respective parameters. The superior performance of synthetic transferosomes may be attributed to their well-defined composition and optimized formulation characteristics, which allow better control over physicochemical properties. In contrast, herbal transferosomes showed comparatively higher bioavailability and drug delivery efficiency. Enhanced bioavailability was reported in 20% of the studies (10/50 articles), while improved drug delivery efficiency was observed in 18% (9/50 articles). These effects may be associated with phytoconstituents that provide natural bioenhancing and synergistic therapeutic activities. Several formulation challenges were also identified. In herbal transferosomes, extract variability was the major challenge, reported in 28% of the studies (14/50 articles), followed by formulation instability in 18% (9/50 articles). These issues are mainly related to the complex and variable nature of plant-derived constituents. Synthetic transferosomes, on the other hand, showed greater challenges related to scalability (27%; 13/50 articles), vesicle size control (20%; 10/50 articles), and encapsulation efficiency (18%; 9/50 articles). These challenges are commonly associated with formulation optimization and large-scale manufacturing. Reproducibility issues were observed in both herbal and synthetic systems with similar frequencies. The improved delivery efficiency observed in herbal transferosomes may also be due to synergistic interactions among phytoconstituents. Terpenes such as limonene, menthol, and cineole may enhance membrane fluidity and vesicle deformability, while flavonoids such as quercetin & curcumin may improve therapeutic efficacy.

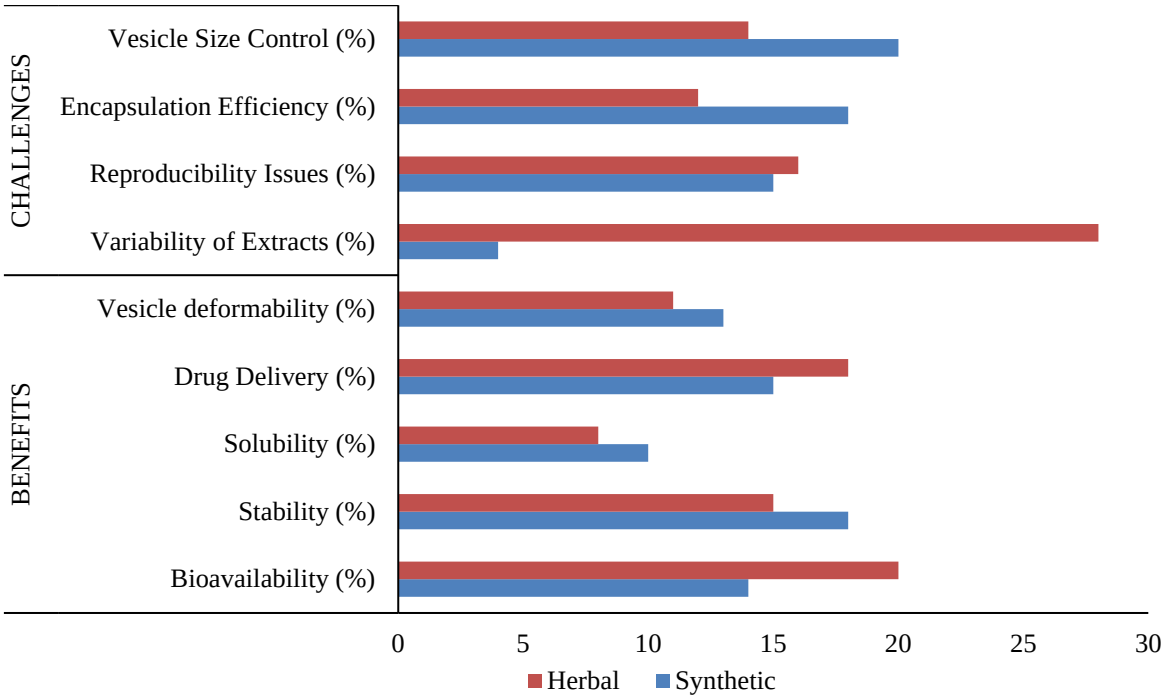

Figure 7: Comparison of Benefits and Challenges of Herbal & Synthetic Transferosomes

Table 4: Comparison of Benefits and Challenges of Herbal & Synthetic Transferosomes

BENEFITS						
Formulation	**Permeability (%)**	**Bioavailability (%)**	**Stability (%)**	**Solubility (%)**	**Drug Delivery (%)**	**Vesicle deformability (%)**
Synthetic	30	14	18	10	15	13
Herbal	28	20	15	8	18	11
CHALLENGES						
	Formulation Instability (%)	**Variability of Extracts (%)**	**Reproducibility Issues (%)**	**Encapsulation Efficiency (%)**	**Vesicle Size Control (%)**	**Scalability (%)**
Synthetic	16	4	15	18	20	27
Herbal	18	28	16	12	14	12

Overall, synthetic transferosomes provide better formulation control and physicochemical stability, whereas herbal transferosomes offer enhanced therapeutic potential and bioavailability but face challenges related to extract variability and formulation stability. Furthermore, herbal transferosomes exhibit greater formulation instability compared to synthetic systems due to the complex and variable nature of phytoconstituents. Polyphenols, flavonoids, alkaloids and terpenoids are more susceptible to oxidation, hydrolysis, photodegradation and interaction with phospholipid bilayers during storage. Variability in phytochemical composition caused by geographical origin, harvesting conditions and extraction methods may further affect vesicle integrity, encapsulation efficiency and reproducibility. In contrast, synthetic transferosomes contain chemically defined active pharmaceutical ingredients with more predictable physicochemical behavior, resulting in comparatively improved formulation stability and reproducibility.

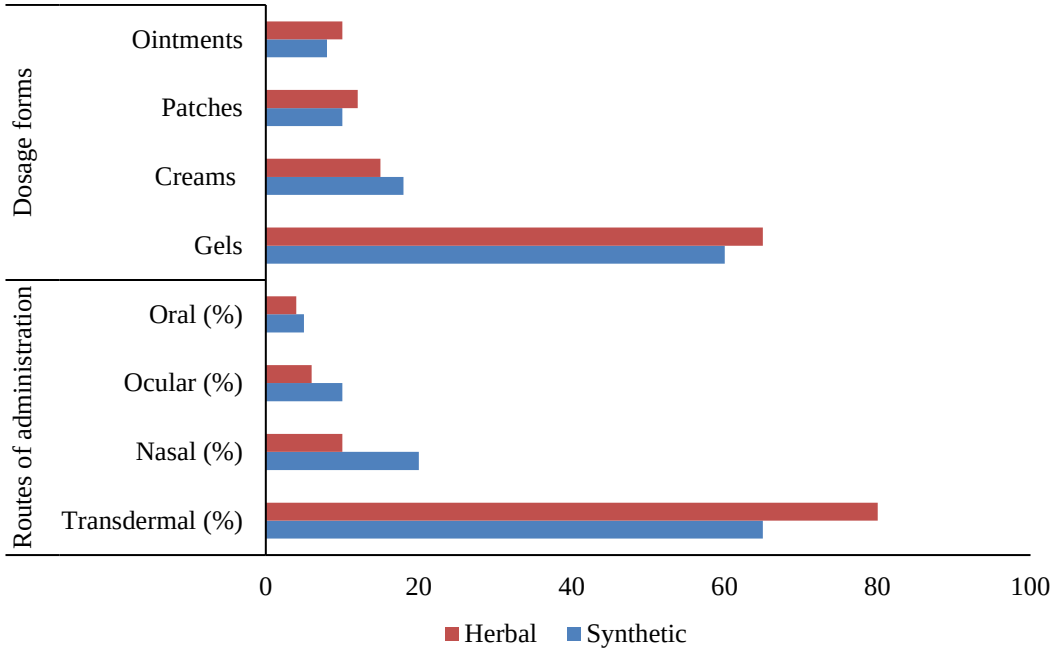

Figure 8: Percentage distribution of synthetic and herbal transferosomal formulations for various routes of administration and dosage forms

Comparative percentage distribution of herbal and synthetic transferosome formulations based on routes of administration and dosage forms

Herbal and synthetic transferosomes share an ultradeformable vesicular structure but differ in composition and therapeutic emphasis. Herbal systems incorporate phytoconstituents with antioxidant, anti-inflammatory, and wound-healing properties, thereby improving solubility, membrane interactions, and local tolerability. Synthetic transferosomes, formulated with defined APIs and synthetic edge activators, allow better control over vesicle deformability, release kinetics & pharmacokinetic predictability.

Table 5: Comparative percentage distribution of herbal and synthetic transferosome formulations based on routes of administration and dosage forms

Routes of Administration				
Formulation	**Transdermal**	**Nasal**	**Ocular**	**Oral**
Synthetic	65 (%)	20 (%)	10 (%)	5 (%)
Herbal	80 (%)	10 (%)	6 (%)	4 (%)
Dosage forms				
	Gels	**Creams**	**Patches**	**Ointments**
Synthetic	60 (%)	18 (%)	10 (%)	8 (%)
Herbal	65 (%)	15 (%)	12 (%)	10 (%)

As shown in Figure 8, the transdermal route dominates the literature for both categories, accounting for 80% of herbal (40 out of 50 articles) and 65% of synthetic formulations (32 out of 50 articles). Nasal (10% herbal; 20% synthetic), ocular (6% herbal; 10% synthetic), and oral (4% herbal; 5% synthetic) routes are less explored. Figure 3 further indicates that gels are the most widely used dosage form (65% herbal; 60% synthetic), followed by creams, patches and ointments. Overall, the data confirm that transdermal gel-based transferosomes are the most extensively studied and therapeutically promising systems among routes and vesicular carriers. The widespread use of the transdermal route in both herbal (80%) and synthetic (65%) transferosomal systems may be attributed to the ultra-deformable nature of transferosomes, which enables efficient penetration through the stratum corneum and skin lipid matrix. A deeper critical analysis of physiological barriers reveals that transferosomal performance differs significantly between transdermal and ocular delivery systems due to the distinct anatomical and biological characteristics of the skin and eye. In transdermal delivery, the primary barrier is the stratum corneum, which consists of densely packed keratinized cells embedded within a lipid matrix. Transferosomes effectively overcome this barrier through their ultra-deformable vesicular structure and an osmotic gradient-driven mechanism, allowing them to squeeze through intercellular spaces much smaller than their own diameter without rupturing. Additionally, the skin provides a comparatively larger surface area for absorption and a longer residence time, which favor sustained drug release and prolonged therapeutic action. In contrast, ocular delivery presents multiple dynamic physiological barriers that significantly limit drug retention and absorption. The eye possesses protective mechanisms such as continuous tear turnover, blinking reflex, nasolacrimal drainage, and tight corneal epithelial junctions, all of which rapidly eliminate administered formulations from the ocular surface. Furthermore, the cornea exhibits selective permeability, with the epithelium restricting hydrophilic molecules and the stroma limiting lipophilic compounds, thereby reducing overall drug permeation. Although transferosomes enhance ocular penetration through improved deformability and membrane interaction, their residence time remains comparatively shorter than in transdermal systems. Consequently, ocular transferosomal formulations often require additional strategies such as mucoadhesive polymers, in situ gels, or viscosity enhancers to improve precorneal retention and therapeutic efficacy. Therefore, while transferosomes demonstrate substantial advantages in both routes, transdermal delivery remains more efficient and has been more extensively explored due to reduced physiological clearance, improved vesicle retention, and enhanced sustained drug delivery.

CONCLUSION

This systematic comparative review highlights the distinct advantages and limitations of herbal and synthetic transferosome systems in advanced drug delivery applications. The findings indicate that synthetic transferosomes generally provide better control over formulation parameters, resulting in improved permeability, stability, solubility, and vesicle deformability. These characteristics make synthetic systems more predictable and reproducible during formulation development and characterization. However, challenges such as scalability, vesicle size control, and encapsulation efficiency remain significant barriers, particularly during large-scale manufacturing and industrial translation. In contrast, herbal transferosomes demonstrate enhanced bioavailability and drug delivery efficiency, primarily due to the presence of multiple phytoconstituents that exhibit synergistic pharmacological activities and natural bioenhancing properties. These characteristics enhance therapeutic potential and may support the development of safer, more biocompatible drug delivery systems. Nevertheless, herbal formulations face notable challenges, including variability in plant extracts and formulation instability, which can affect consistency, reproducibility, and long-term stability. The analysis also reveals that the transdermal route remains the most widely explored method for transferosome-based delivery, with gel formulations being the most commonly used dosage form due to their ease of application & ability to enhance drug permeation through skin. Overall, both herbal and synthetic transferosomes offer promising opportunities for improving drug delivery

performance. Future research should focus on optimizing formulation strategies, particularly the selection and ratio of edge activators, improving the standardization of herbal extracts, and developing scalable manufacturing approaches. Addressing these challenges will be essential for enhancing the stability, reproducibility, and clinical translation of transferosome-based drug delivery systems. Future optimization of transferosomal systems should focus on improving vesicle stability and storage performance to facilitate clinical translation. Lyophilization may enhance long-term stability of both herbal and synthetic transferosomes. In herbal formulations, antioxidants such as BHT or α-tocopherol may reduce oxidative degradation of phytoconstituents. In contrast, synthetic systems may benefit from optimized lipid composition and cryoprotectant-assisted stabilization to minimize vesicle aggregation and drug leakage.

FINANCIAL ASSISTANCE
NIL

CONFLICT OF INTEREST
The authors declare no conflict of interest.

AUTHOR CONTRIBUTION
Vijaykumar Meti and Dattatreya planned and conceptualized the manuscript. Dattatreya & Sai Teja K designed the figures, conducted the literature review, and drafted the manuscript. Based on an analysis of various data sources, Parwati Naikar, Dattatreya, and Sai Teja K drafted a literature review. Vijaykumar Meti and Dattatreya evaluated data from multiple research papers.

DECLARATION OF USE OF AI TOOLS
The authors used ChatGPT to assist with language editing, improve readability, and generate high-resolution images. All content, analysis, and conclusions were reviewed and verified by the authors. The authors take full responsibility for the originality, accuracy, and integrity of the work.

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