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Review Article

Herbal phytosomal gels: Benefits, challenges, and future directions: A review

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Abstract

The growing interest in herbal medicine has led to significant advancements in drug delivery, particularly with the development of phytosomal gels. These formulations combine herbal extracts with phospholipids to enhance the solubility, stability, and absorption of beneficial plant compounds, thereby improving their effectiveness when applied to the skin or absorbed into the body.

Phytosomal technology forms a protective complex around herbal compounds, facilitating better absorption and ensuring prolonged therapeutic effects. This article explores the formulation, working mechanism, and applications of phytosomal gels in medicine and skincare. It also highlights essential quality control measures for ensuring safety and effectiveness, along with the challenges associated with these formulations and potential strategies to overcome them.

Despite their advantages, phytosomal gels still face several challenges. Stability concerns, high manufacturing costs, and stringent regulatory guidelines pose significant barriers to large-scale production and commercialization. To address these challenges, researchers must refine formulation techniques, reduce production costs, and streamline regulatory approval processes.

Future research should focus on scientifically validating the benefits of phytosomal gels while ensuring compliance with safety standards. Enhancing affordability and maintaining high quality will improve accessibility and adoption. As interest in natural remedies continues to grow, phytosomal gels have the potential to revolutionize medicine and skincare by integrating traditional herbal knowledge with modern scientific advancements for better therapeutic outcomes.

Keywords: Phytosomal technology, Bioavailability enhancement, Herbal drug delivery, Formulation challenges, Therapeutic & cosmetic applications.

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1. Introduction

The use of plant-based medicines has been steadily increasing in the West, despite a decline over the past two centuries due to the rise of synthetic drugs.[1] However, in many developing countries, traditional medicine remains the backbone of healthcare, with well-established systems like Ayurveda, Unani, Siddha, and Traditional Chinese Medicine (TCM) continuing to play a significant role in treating various ailments.[2] The history of medicinal plant use dates back thousands of years, with ancient civilizations such as China and Egypt documenting the therapeutic properties of herbs. Additionally, indigenous cultures across Africa, the Americas, and other regions have long relied on botanicals for healing and disease prevention. These traditional practices often involve using specific plant parts, including seeds, berries, flowers, leaves, bark, and roots, to create herbal formulations to promote health and well-being. This approach, known as herbal medicine or phytomedicine, remains a vital part of global healthcare, often complementing modern pharmaceuticals.[3]

Herbal medicine, or phytotherapy, involves studying plants for therapeutic and nutritional benefits, traditionally using crude preparations like tinctures, teas, powders, syrups, and extracts.[4] Valued for affordability, fewer side effects, and natural benefits, herbal medicines remain essential in traditional and modern healthcare, with WHO estimating 80% of the global population relies on them.[5] These plant-based remedies contain bioactive compounds with antioxidant, anti-inflammatory, antimicrobial, and wound-healing properties.[6] However, low bioavailability limits their effectiveness, particularly in topical and oral applications.[7] Modern advancements have improved usability through tablets, patches, and gels, while future innovations focus on

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enhancing bioavailability with phytosomal gels for better therapeutic outcomes.[8]

Phytosomes are advanced delivery systems that enhance the bioavailability of plant-based compounds by complexing them with phospholipids. However, their widespread acceptance faces challenges, including stability issues that affect shelf life and efficacy, high manufacturing costs due to sophisticated production techniques and high-quality materials, and regulatory hurdles requiring extensive research and compliance. Despite these obstacles, the market for phytosome-based products is growing. The global phytosterols market, closely related due to its focus on plant-based compounds, was valued at approximately USD 709.6 million in 2019 and is projected to reach USD 1.38 billion by 2027, with a compound annual growth rate (CAGR) of 8.7%, driven by increasing consumer demand for natural and effective health solutions.[9] Hence, this review aims to explore advancements, benefits, challenges, and potential applications of herbal-based phytosomes in enhancing bioavailability, stability, and efficacy.

2. Phytosomes: An Innovative Delivery System

Phytosomes are advanced drug delivery systems that enhance the solubility, stability, and absorption of herbal extracts by complexing them with phospholipids, significantly improving bioavailability and therapeutic efficacy.[10] Unlike traditional extracts with poor membrane penetration, phytosomes facilitate better absorption, ensuring enhanced therapeutic outcomes. When incorporated into gels, they provide stable topical formulations for direct skin delivery, leveraging the benefits of hydration, ease of application, and controlled release.[11] These formulations are increasingly preferred in skincare and therapeutic applications, offering natural alternatives that rival synthetic products in effectiveness and stability.[12] Many herbal actives, such as flavonoids and polyphenols, suffer from poor solubility and limited permeability, reducing their efficacy. Phytosome technology overcomes these limitations by forming lipid-compatible complexes that enhance membrane interaction, enabling lower dosages and reduced application frequency while maintaining therapeutic potency.[13]

Phytosomes offer several advantages, including enhanced bioavailability, improved solubility, and better absorption of herbal compounds, leading to increased therapeutic efficacy at lower doses. Their lipid-compatible structure allows for better interaction with biological membranes, ensuring efficient delivery in both oral and topical formulations. Additionally, phytosomal formulations provide controlled release, improved stability, and higher patient compliance, making them suitable for skincare and pharmaceutical applications. However, they also have limitations, such as high production costs, complex formulation processes, and potential stability issues during storage. Regulatory challenges and the need for extensive research and standardization further hinder their widespread adoption. Despite these drawbacks, the growing demand for natural and effective drug delivery systems continues to drive innovation in phytosome technology.[14]

3. Mechanism of action and Composition of Phytosomes

Phytosomes integrate with biological membranes, improving solubility, absorption, and bioavailability. Phospholipids protect active compounds from degradation caused by light, heat, and oxidation, ensuring long-term stability.[15]

3.1. Mechanisms of phytosomal technology

1. **Phospholipid encapsulation:** Herbal compounds (e.g., flavonoids, terpenoids, polyphenols) bind with phospholipids like phosphatidylcholine, forming lipid-compatible complexes that enhance fat solubility and membrane penetration.[16]
2. **Improved absorption:** The lipid-soluble nature of phytosomes allows active ingredients to pass through cell membranes more efficiently, increasing bioavailability and absorption rates.
3. **Greater stability:** Phytosomes protect bioactive compounds from environmental degradation (heat, light, air) and enable controlled release, prolonging their therapeutic effects.[16]
4. **Stronger molecular interaction:** Phytosomes form chemical bonds with phospholipids, ensuring greater stability and integrity than liposomes, which encapsulate actives in vesicles. This enhances efficacy at lower doses, making phytosomes valuable in skincare, nutraceuticals, and pharmaceuticals. By improving lipid compatibility and preventing degradation, they provide long-lasting therapeutic effects, ideal for medicinal and cosmetic applications.[17]

3.2. Composition of herbal phytosomal gels

Phytosomal gels combine herbal phytosomes with gel bases for better skin penetration and sustained effects.

1. **Selection of herbal ingredients:** Herbal actives are chosen for their therapeutic properties.
2. **Phospholipid complexation:** Herbal actives are mixed with phospholipids through: Solvent Evaporation: Organic solvents dissolve the mixture, which is then evaporated to form a phytosome layer. Anti-Solvent Precipitation: Adding an anti-solvent precipitates the complex, enhancing stability.[18]
3. **Gel base selection:** A suitable gel base ensures consistency and stability: Carbopol: Provides smooth, transparent texture. Hydroxyethylcellulose (HEC): Increases thickness and clarity. Xanthan Gum: A natural stabilizer for consistency.
4. **Incorporation of phytosomes into gel:** Phytosomes are dispersed into the gel base through:
5. **Homogenization:** A high-shear mixer ensures even distribution.

6. **pH adjustment:** pH is set to match skin (5–5.5) for compatibility.
7. **Preservatives & stabilizers:** Preservatives like phenoxyethanol extend shelf life, while stabilizers prevent separation.[19]

3.3. Quality control tests

1. **Viscosity & texture:** These assessments determine the gel's spreadability and user experience. A gel with appropriate viscosity ensures ease of application and optimal skin coverage. Texture analysis evaluates attributes like smoothness and consistency, which are crucial for patient compliance and therapeutic effectiveness.[20]
2. **pH measurement:** The pH level of the gel is measured to confirm its compatibility with skin conditions, typically aiming for a pH between 5 and 5.5. Maintaining this pH range helps prevent skin irritation and supports the stability of the herbal actives.[21]
3. **Particle size & stability:** Evaluating the particle size of the phytosomal complexes ensures uniform distribution within the gel, which is vital for consistent drug delivery. Stability tests, such as centrifugation, assess the gel's resistance to phase separation under various conditions, indicating its physical stability over time.[22]
4. **Drug release & permeation:** In vitro studies are conducted to assess the controlled release of herbal actives from the gel and their permeation through the skin. These tests help determine the gel's effectiveness in delivering therapeutic concentrations to the target site.[23] By rigorously performing these QC tests, manufacturers can ensure that herbal phytosomal gels meet the necessary standards for safety, efficacy, and quality, thereby providing reliable therapeutic options for consumers.
5. **Packaging & storage:** Phytosomal gels are stored in airtight, opaque containers to protect against light, air, and moisture. Cool storage conditions ensure long-term stability.[24]

3.4. Mechanisms of action in skin delivery of phytosomal gels

As shown in **Figure 1**, Phytosomal gels deliver active herbal compounds to the skin using a combination of mechanisms that enhance penetration, bioavailability, and sustained release, making them highly effective for topical applications.

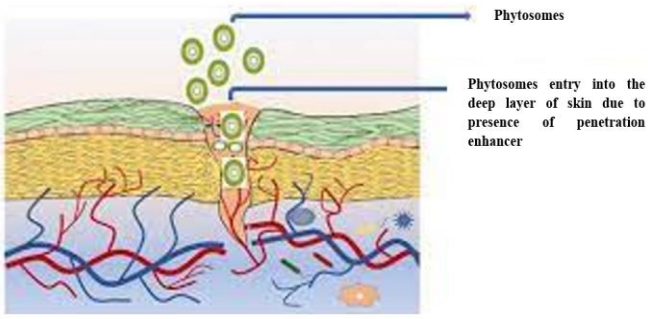

Figure 1: Mechanism of Action in skin delivery of Phytosomes as a penetrating enhancer

Here are the primary mechanisms through which phytosomal gels act in skin delivery:

1. **Enhanced permeation through phospholipids:** Phytosomal gels, created by complexing herbal compounds with phospholipids like phosphatidylcholine, enhance the absorption and bioavailability of bioactive ingredients. These complex mimics the skin's lipid structure, allowing active compounds to better penetrate the stratum corneum. The skin's lipid layer readily absorbs lipid-soluble phytosomal complexes, improving permeation compared to traditional water-based extracts.[25]
   Studies have shown the effectiveness of this approach in enhancing solubility, stability, and absorption of herbal compounds. Telange et al. developed a mangiferin-phospholipid complex (MPLC), increasing solubility (~32-fold), dissolution (~98%), and permeation (~97%), leading to a 10-fold boost in oral bioavailability. Similarly, Saoji et al. formulated Bacopa Naturosome (BN), achieving a 20-fold solubility increase and >90% permeation. Shriram et al. improved silymarin's bioavailability by 6-fold using phytosomal technology. Hashemzadeh confirmed through computational studies that phytosome formation enhances the stability and penetration of polyphenols like EGCG, luteolin, and resveratrol.[26-29]
   These findings highlight phospholipid complexation as a promising strategy for improving poorly soluble herbal compounds. Phosphatidylcholine (PC) consistently enhances permeation and bioavailability, as demonstrated in formulations of mangiferin, Bacopa, and polyphenols
2. **Improved stability and bioavailability**: Phytosomes, formed by complexing herbal compounds with phospholipids like phosphatidylcholine, enhance both stability and bioavailability. Phosphatidylcholine protects bioactive compounds from oxidation, hydrolysis, and UV degradation, ensuring they remain intact and effective. By encapsulating herbal actives, phytosomes prevent degradation, preserving their potency until they reach the target site.
   Additionally, phospholipid complexes improve bioavailability by increasing solubility and facilitating better absorption. Their lipid-compatible structure

resembles cell membranes, allowing easy penetration through the skin or gastrointestinal tract. For instance, silymarin phytosomes showed a 6-fold boost in oral bioavailability and significant hepatoprotection. Similarly, apigenin-phospholipid phytosomes improved solubility by 36-fold, enhancing bioavailability and antioxidant effects.[26]

By improving dissolution rates, phospholipid complexes ensure a higher percentage of active compounds remain effective after administration. Thus, phosphatidylcholine not only stabilizes herbal compounds but also enhances their absorption and therapeutic potential.[28]

3. **Controlled release and prolonged effect:** Phytosomal gels provide controlled release and a prolonged therapeutic effect by gradually delivering active compounds over time. Phospholipids enable sustained release, reducing application frequency while enhancing efficacy and minimizing irritation.

   For instance, Hou et al. developed a mitomycin C–soybean phosphatidylcholine (MMC–SPC) phytosome, which showed a biphasic release pattern—an initial burst followed by sustained release—enhancing cytotoxicity and antitumor efficacy. Similarly, Zhang et al. formulated curcumin-phytosome-loaded chitosan microspheres (Cur-PS-CMs), improving bioavailability and retention time in rats through slower drug release and an extended half-life. Molaveisi et al. designed a nanophytosome system for vitamin D3, ensuring greater stability and controlled release via a Fickian diffusion mechanism.[30-32]

   Additionally, Salian et al. developed resveratrol phytosomes (RSVP) and resveratrol-piperine phytosomes (RPP), which prolonged circulation over 24 hours in rats with myocardial infarction, improving heart function, reducing inflammation, and boosting antioxidant levels.[33]

   The use of phospholipids in phytosomes stabilizes active ingredients, protecting them from degradation while allowing sustained release at the target site. This controlled delivery system significantly enhances bioavailability and therapeutic efficacy.

4. **Penetration-enhancing effect of phospholipids:** Phospholipids in phytosomes serve as penetration enhancers, disrupting the stratum corneum's tight junctions to improve the skin's absorption of active compounds. Dong et al. developed lecithin/chitosan nanoparticles containing a baicalein-phospholipid complex, which significantly increased transdermal retention and penetration. Similarly, Ebada et al. formulated a rhein-phospholipid complex (RH-PLC), achieving a 3.3-fold increase in skin permeability and deeper penetration.[34,35]

   In another study, Xu et al. designed an insulin-phospholipid complex with deformable nanovesicles, enhancing insulin permeability and bioavailability. Additionally, Alsaidan et al. optimized lipid-polymer hybrid nanoparticles for hydrocortisone acetate, improving both skin permeation and anti-inflammatory effects.[36,37]

   These findings highlight the crucial role of phospholipids in enhancing the penetration and therapeutic efficacy of bioactive compounds in transdermal drug delivery.

5. **Increased affinity for skin lipids:** Phytosomes, especially those using phosphatidylcholine, enhance the delivery and efficacy of active compounds due to their natural affinity for skin lipids. Their amphiphilic nature allows them to integrate with the skin's lipid matrix, promoting deeper penetration, improved hydration, and reduced transepidermal water loss (TEWL).

   Rahmi et al. formulated a Mangkokan leaf phytosome lotion, which significantly enhanced hair growth, demonstrating effectiveness in skin and hair applications. Similarly, Visht et al. developed eucalyptus oil phytosomes, achieving high encapsulation efficiency and stability, with acetone producing the smallest, most stable particles.[38,39]

   For wound care, Lim et al. designed a Moringa oleifera phytosome, which promoted cell migration and proliferation without cytotoxicity, emphasizing targeted skin delivery. Additionally, Abd El-Fattah et al. developed quercetin-loaded phytosomes, showing improved bioavailability and therapeutic efficacy in an ovariectomized rat model.[40,41]

   These findings highlight phytosomes strong skin-lipid interaction, leading to better absorption, sustained release, and enhanced therapeutic effects.

6. **Targeted delivery of active herbal compounds:** Phytosomal formulations enhance the targeted delivery of herbal compounds, maximizing therapeutic efficacy while minimizing side effects. Danish, highlights their role in delivering anti-inflammatory and antioxidant agents to specific skin layers for improved localized effects.[42]

   For cancer treatment, Ochi et al. developed a nano-liposome system co-encapsulating silibinin and glycyrrhizic acid, enhancing cytotoxicity and synergistic effects against liver cancer cells. Setyowati et al. formulated Acanthus ilicifolius leaf extract-loaded nanophytosomes, improving bioactive compound delivery and controlled release.[43,44]

   Phytosomes also enhance transdermal drug delivery. Sasongko optimized bitter melon extract-loaded phytosomes, increasing skin penetration. Similarly, Wanjiru et al. encapsulated Moringa oleifera polyphenols, demonstrating potent cytotoxic effects against 4T1 breast cancer cells.[45,46]

These studies are tabulated in **Table 1** to confirm phytosomes' ability to improve stability, bioavailability, and targeted drug delivery, ensuring better therapeutic outcomes with fewer side effects.

Table 1: Impact of phytosomes on permeation, stability, release, penetration, skin affinity, and targeted delivery

Herbal Plant/Compound	Method	Key Focus/Effect	Phospholipid Role	Phytosome Characteristics/Results
Mitomycin C-Soybean Phosphatidylcholine (MMC-SPC)	Phytosome Complex (Solvent Evaporation & Nanoprecipitation)	Enhanced Cytotoxicity & Antitumor Efficacy	Phytosomes increase bioavailability and provide sustained release	210.87 nm, Zeta Potential: -33.38 mV, Biphasic release, High stability
Curcumin	Phytosome-Loaded Chitosan Microspheres	Improved Bioavailability & Prolonged Effect	Phytosomes enhance stability and controlled release	23.21 µm, 1.67-fold increase in absorption, Prolonged half-life of 3.16h
Vitamin D3	Nanophytosome System	Enhanced Stability & Controlled Release	Phytosomes protect vitamin D3 and improve its bioavailability	Improved solubility, Antioxidant activity, Fickian diffusion release
Resveratrol	Phytosome System (Co-Loaded with Piperine)	Cardioprotective Effect in MI Induced Rats	Phytosomes increase drug stability and prolong circulation	Zeta Potential: -33.33 mV, Particle Size: 20.98 nm, Prolonged circulation
Baicalein	Lecithin/Chitosan Nanoparticles	Improved Skin Penetration & Retention	Phospholipid complex enhances skin penetration	84.5% Entrapment efficiency, Efficient skin penetration, No irritation
Rhein	Rhein-Phospholipid Complex (RH-PLC)	Enhanced Skin Permeability	Phospholipids improve solubility and skin penetration	196.6 ± 1.6 nm, Zeta Potential: -29.7 mV, 3.3-fold increase in permeability
Insulin	Phospholipid Complex with Nanovesicles	Enhanced Permeability for Buccal Delivery	Phospholipids improve protein permeation and bioavailability	Higher bioavailability (15.53%), No mucosal irritation
Hydrocortisone Acetate	Lipid Polymer Hybrid Nanoparticles	Enhanced Skin Delivery for Anti-inflammatory Effect	Phytosomes enhance skin permeation and targeted delivery	Higher permeation rate, Anti-inflammatory activity
Mangkokan Leaf Extract	Phytosome Lotion	Improved Hair Growth Activity	Phytosomes enhance bioavailability and targeted delivery	289 nm, 99.76% entrapment efficiency, Superior hair growth compared to minoxidil
Eucalyptus Oil	Phytosome System	Improved Delivery of Essential Oils	Phytosomes enhance stability and controlled release	Particle Size: 71.76–197.36 nm, High stability
Moringa Oleifera	Phytosome System for Wound Healing	Enhanced Delivery to Skin Layers	Phytosomes increase skin penetration and localized therapeutic effects	198 ± 21 nm, Zeta Potential: -28.30 mV, High fibroblast cell migration
Quercetin	Phytosome Nanoparticles	Improved Bioavailability & Hormone Replacement Therapy	Phytosomes improve stability and absorption	70 ± 7.44 nm, 98.4% encapsulation efficiency, Improved calcium & phosphorus levels
Bitter Melon Extract	Phytosome Transdermal Delivery	Enhanced Skin Penetration	Phytosomes enhance transdermal delivery	282.3 ± 16.4 nm, Zeta Potential: -39.2 mV, 90.06% entrapment efficiency
Moringa Oleifera Polyphenols	Phytosome Encapsulation for Cancer	Targeted Anti-cancer Activity	Phytosomes improve drug stability and controlled release	296 ± 0.29 nm, Zeta Potential: -40.1 mV, 90.32% entrapment efficiency
Silibinin and Glycyrrhizic Acid	Nano-Liposome System	Enhanced Efficacy for Hepatocellular Carcinoma Therapy	Phytosomes increase bioavailability and stability	46.3 nm, 24.37% and 68.78% entrapment efficiency, IC50 of 48.68 µg/ml
Acanthus ilicifolius	Nanophytosome Formulation	Enhanced Bioactive Compound Delivery	Phytosomes improve bioavailability and controlled release	120.7–125.8 nm, Zeta Potential: -26.6 mV, best adsorption efficiency

3.5. Therapeutic applications of herbal phytosomal gels

Herbal phytosomal gels have gained attention for their enhanced skin permeability, stability, and targeted delivery, making them ideal for a variety of therapeutic applications in dermatology and skincare.[47] Here are some key applications:

3.5.1. Anti-inflammatory and analgesic treatments

Phytosomal formulations enhance the bioavailability and therapeutic effects of herbal compounds, making them effective for arthritis, muscle pain, and inflammation. Baradaran et al. found curcumin nano-phytosomes (15 mg/kg) significantly improved antioxidant enzyme levels and reduced carrageenan-induced inflammation ($p < 0.05$).[48]

Gungor-Ak et al. developed berberine-phospholipid complexes (BPCs, 209 mg/kg), demonstrating anti-inflammatory, analgesic, and antipyretic effects. Senthil Kumar et al. formulated Tinospora cordifolia phytosomes (454.2 ± 8.1 nm vesicle size, −43.1 ± 7.5 mV zeta potential), achieving 94.7% drug release with strong anti-inflammatory and analgesic properties.[49,50]

For arthritis and rheumatism, Das & Kalita developed Rutin-phytosomes (RN-Ps), improving transdermal absorption (33% vs. 13%) compared to free Rutin. These findings highlight phytosomes' potential in pain and inflammation management.[51]

3.5.2. Antioxidant and anti-aging skincare

Phytosomal formulations improve skin penetration and bioavailability of antioxidant-rich herbs like Camellia sinensis, Ginkgo biloba, and Silybum marianum, reducing oxidative stress and enhancing skin elasticity.[52]

Joshua et al. developed an anti-aging phytosomal gel with coconut water, Aloe vera, grape seed extract, vitamin E, and jojoba oil. The optimized formulation (F2) showed strong antioxidant activity (IC50 = 47.0 µg/ml) and remained stable for 45 days. Similarly, Patidar et al. created a gingerol oil–Carica papaya phytosomal serum, achieving 42.26% antioxidant activity and three-month stability.[53,54]

Damle & Mallya formulated a polyherbal phytophospholipid cream with Citrus auranticum and Glycyrrhiza glabra, showing 87.99% DPPH scavenging and 28.02% anti-elastase activity, enhancing polyphenol retention. Kolambe developed a crocin-rich phytosomal gel with petroselinic acid, providing SPF 15.09 and increasing skin moisture (30.08% to 45.59% in 5 hours), offering hydration and moderate sun protection.[55,56]

These studies highlight phytosomes potential in anti-aging, hydration, and skin protection.

3.5.3. Wound healing and skin regeneration

Phytosomal formulations improve bioavailability of wound-healing herbs like Centella Asiatica and Aloe vera, promoting collagen synthesis and tissue regeneration.[57]

Varadkar & Gadgoli developed a crocetin-loaded phytosomal gel, reducing epithelization time from 26 to 9 days and increasing wound tensile strength in rats. Mazumder et al. formulated a sinigrin–phytosome complex (153 ± 39 nm, 69.5% efficiency), accelerating wound closure to 42 hours, outperforming free sinigrin (71%), and showing cytocompatibility with HaCaT cells and antitumor activity against A-375 cells.[5758,59]

Dashti et al. evaluated eugenol-loaded phytosomal hydrogels, which reduced inflammation markers (COX-2, NF-κB, Nrf2) and exhibited antibacterial activity, performing comparably to mupirocin. Al-Samydai et al. developed PEGylated 6-gingerol nanophytosomes (150.16 ± 1.65 nm, 34.54% encapsulation efficiency), which downregulated cytokines, promoted wound healing, and showed anticancer potential.[60,61]

These findings emphasize phytosomes effectiveness in targeted drug delivery and enhanced wound recovery, especially for infected and chronic wounds.

3.5.4. Antimicrobial and antifungal treatments

Phytosomal gels with Azadirachta indica (neem) and Calendula officinalis enhance antimicrobial activity by improving bioavailability and skin penetration, making them effective against bacterial and fungal infections. Raj et al. developed an Ocimum basilicum phytosomal gel, showing better skin absorption, antimicrobial effects, and stability. Efimova & Ostroumova modified Amphotericin B (AmB)-loaded liposomes, improving antifungal efficacy while reducing toxicity.[62,63]

Jagtap et al. formulated Adiantum capillus-veneris phytosomes, enhancing drug dissolution and antimicrobial potency, confirmed by IR, TEM, and DSC analysis. Rani et al. optimized Murraya koenigii phytosomes (236 nm, 75.1% entrapment efficiency), demonstrating improved antidiabetic activity in diabetic rats. These studies highlight phytosomes' potential in treating infectious skin conditions and metabolic disorders.[64,65]

3.5.5. Skin brightening and pigmentation correction

Phytosomal gels with Glycyrrhiza glabra, Camellia sinensis, and Curcuma longa enhance skin brightening and depigmentation by improving melanin reduction and antioxidant activity. Priani et al. developed a cocoa pod extract phytosome serum (90.5% entrapment efficiency), demonstrating strong antioxidant (IC50: 17.21 ppm) and tyrosinase inhibition (IC50: 199.98 ppm), comparable to Hadalabo Ultimate Whitening Milk. Sahin et al. formulated nano-phytosomes for phycocyanin (Phy), achieving 81.92%

entrapment efficiency and enhanced intestinal bioaccessibility, supporting its use as a skin-lightening agent.[66,67]

Mohapatra et al. reviewed phytosomes in dermatology, emphasizing improved solubility, stability, and skin penetration, especially for ellagic acid and eugenol-based formulations. Zhu et al. explored tetrahydro curcumin (THCu) production, highlighting enzymatic and microbial transformations for better stability and skin-whitening effects. These findings confirm phytosomes' potential in cosmeceuticals for hyperpigmentation correction and skin tone enhancement.[68,69]

3.5.6. Moisturizing and hydrating formulations

Phytosomal gels with Aloe vera and Chamomilla recutita enhance hydration, skin barrier repair, and reduce TEWL through phospholipid-based moisture retention.[53] Anwar & Farhana developed a green tea extract phytosome-loaded microsphere system, achieving 50.61% entrapment efficiency, -48.2 mV zeta potential, and sustained release over 4 hours, improving stability and bioavailability. Takle et al. formulated a multi-functional herbal cream with aloe vera, neem, tulsi, and cucumber, combining moisturizing, antimicrobial, and anti-inflammatory benefits.[70,71]

Salunkhe et al. reviewed herbal lotions with aloe vera, coconut milk, honey, and lavender, emphasizing hydrating, antioxidant, and anti-inflammatory properties in natural skincare. These findings highlight phytosomes' potential in moisturizing, soothing, and promoting skin health through enhanced bioavailability and natural ingredients.[72] As shown in **Table 2**, The table outlines various phytosomal gel formulations and their benefits for different skin conditions.

4. Challenges in Formulation and Application of Herbal Phytosomal Gels

Despite the potential of herbal phytosomal gels, several challenges exist in their formulation and application. These challenges include stability issues, cost, regulatory concerns, and complex formulation requirements.[73] Here's an overview of key obstacles which are tabulated in **Table 3** for various challenges in formulation and application of Herbal Phytosomal gels.

4.1. Stability and shelf-life

Phytosomal formulations are prone to environmental degradation from heat, light, and oxygen, affecting both herbal actives and phospholipids. To enhance stability and efficacy, strategies like airtight, opaque packaging and stabilizers are essential. Khan et al. optimized polyherbal phytosomes (PHP) using Annona squamosa and Cinnamomum tamala extracts, achieving high entrapment efficiency and superior skin permeation in a Carbopol 934 gel. Stability studies confirmed PHP gel robustness. Similarly, Djekic et al. analyzed escin β-sitosterol (ES) phytosome hydrogels, showing that higher active concentrations increased viscosity, thixotropy, and prolonged skin retention, maintaining stability for three months with significant antihyperalgesic effects.[11,74]

Table 2: Therapeutic applications of phytosomes and herbal formulations in dermatology

Therapeutic Application	Herbal Extract Used	Phytosome Benefits	Key Effects
Anti-aging	Green tea (Camellia sinensis)	Enhanced antioxidant penetration	Reduces wrinkles, improves elasticity
Skin Brightening	Licorice (Glycyrrhiza glabra)	Improved bioavailability of glabridin	Reduces hyperpigmentation, evens skin tone
Wound Healing	Aloe vera	Increased skin absorption	Accelerates tissue repair, reduces scarring
Anti-inflammatory	Turmeric (Curcuma longa)	Improved curcumin solubility	Reduces redness, soothes irritation
Acne Treatment	Neem (Azadirachta indica)	Enhanced antimicrobial activity	Controls bacterial growth, reduces breakouts
Moisturization	Olive oil phytosomes	Enhanced hydration retention	Deeply nourishes and hydrates skin
Sun Protection	Grape seed extract (Vitis vinifera)	Increased UV protection	Prevents photodamage, enhances SPF efficacy
Antimicrobial	Tea tree oil (Melaleuca alternifolia)	Controlled release for prolonged action	Fights bacteria and fungi, prevents infections
Psoriasis Management	Boswellia serrata	Increased skin permeability	Reduces inflammation, soothes itching
Eczema Relief	Chamomile (Matricaria chamomilla)	Improved penetration of flavonoids	Calms irritated skin, reduces flare-ups

Table 3: Challenges, causes, and solutions in phytosome-based formulations

Challenge	Reason for Challenge	Possible Solutions
Stability Issues (Environmental & Long-Term)	Heat, light, oxygen, and time degrade herbal actives and phospholipids.	Use UV-resistant packaging, antioxidants, stabilizers, and microencapsulation.
High Cost & Supply Variability of Phospholipids	Pharmaceutical-grade phospholipids are expensive and inconsistently available.	Identify cost-effective plant-derived phospholipids and establish standardized sourcing.
Limited Bioavailability & Solubility	Some herbal extracts lack solubility in both aqueous and lipid media, affecting absorption.	Use lipid carriers, co-solvents, surfactants, and self-emulsifying systems.
Complex Extraction & Processing	Herbal extracts require advanced fractionation and solvent selection for optimal bioactivity.	Use eco-friendly and efficient extraction technologies like supercritical fluid extraction.
Formulation Challenges (Viscosity, Retention & pH Optimization)	Achieving optimal gel consistency, spreadability, and skin compatibility requires precise formulation.	Optimize polymer concentration, adjust pH, and select compatible excipients.
Need for Advanced Delivery Systems	Enhancing stability and absorption requires complex nanotechnology-based carriers.	Optimize simple, scalable formulation techniques like liposomes and solid lipid nanoparticles.
Regulatory & Compliance Barriers	Varying global safety, efficacy, and quality standards increase costs and delay market access.	Follow WHO, ICH, and GACP guidelines while implementing QbD for cost-effective compliance.
Batch-to-Batch Inconsistency	Natural variations in plant composition affect potency and reproducibility.	Standardize extraction methods, implement chemometric analysis, and use stringent quality control.
Dermatological Safety & Skin Irritation Risks	Lipid components, herbal actives, or surfactants may cause irritation or allergic reactions.	Conduct safety testing, use mild excipients, and ensure skin compatibility through dermatological studies.
Commercialization & Market Access Limitations	Scaling up production and meeting certification requirements (e.g., halal, sustainability) is challenging.	Develop industry-academic collaborations, implement cost-efficient production, and obtain globally accepted certifications.

Innovative stability solutions include exosome-based formulations. Setiadi et al. developed a photoaging treatment gel with Physalis minima exosomes, demonstrating favorable stability and antioxidant activity. Stability issues also affect traditional herbal preparations. Bilia et al. assessed Hawthorn and Hawkweed tinctures, noting Hawthorn's procyanidins had a t (90) of seven months, while Hawkweed's caffeoyl-quinic acids remained stable for nine months. These findings emphasize the need for formulation optimization and stability studies in phytosomal and herbal product development.[75,76]

4.2. High cost of phospholipids

Phospholipids are essential in phytosomal formulations, enhancing solubility, stability, and dermal permeability of herbal bioactives. However, high-purity grades needed for pharmaceuticals are costly, affecting large-scale production and affordability, especially in price-sensitive markets. Sourcing high-quality phospholipids is also challenging due to supply variability and quality inconsistencies. Shah et al. emphasized the therapeutic benefits of phosphatidylcholine-fortified phytopharmaceuticals, improving solubility, bioavailability, and targeted delivery. Alexander et al. reviewed nanotechnology-based delivery systems like phytosomes, nanoparticles, and transferosomes, addressing solubility and absorption limitations.[77,78]

To tackle cost and supply issues, nanoformulation strategies are being explored. Barani et al. highlighted phytosomes as innovative carriers, improving bio-efficacy while reducing dosage requirements. Despite these advancements, high phospholipid costs remain a barrier to commercialization. Research into cost-effective alternatives and scalable production methods is crucial for the sustainable development of phytosomal formulations.[8]

4.3. Complex formulation process

Developing stable phytosomal gels requires complex formulation techniques, including herbal extract–phospholipid complexation and gel matrix integration. Achieving uniform particle size, stable dispersion, and optimal drug release demands specialized equipment and expertise, increasing production complexity and costs. Joshua et al. demonstrated that phytosomal gels enhance skin penetration and antioxidant efficacy over conventional

creams but require precise optimization. Similarly, Vijayakumar et al. formulated a polyherbal phytosomal gel for pharyngitis, exhibiting anti-inflammatory and antibacterial effects, yet needing advanced techniques like antisolvent precipitation for consistent particle size and entrapment efficiency.[24,79]

Enhancing bioavailability requires rigorous characterization and optimization. Yadav et al. developed Cassia fistula-based phytosomal gels, requiring detailed analysis of particle size, zeta potential, and drug release kinetics for stability and efficacy. Chilka et al. showed Musa paradisica (banana peel) extract phytosomal gels had stronger antioxidant activity than methanol extract gels, highlighting the need for specialized formulation methods. While phytosomal technology improves herbal bioactive delivery, its complex synthesis and analytical demands remain key challenges in large-scale production.[80,81]

4.4. Limited solubility of certain herbal extracts

The low solubility of certain herbal extracts in aqueous and lipid phases challenges phytosomal formulations, requiring solubilizing agents or co-solvents, which may affect stability and compatibility.[15] Karole et al. found that Bombax ceiba–soya lecithin phytosomes significantly improved solubility, bioavailability, and antioxidant activity. Similarly, Solanki et al. reported that Tabernaemontana divaricata fruit phytosomes showed greater antioxidant efficacy and stability than free extracts.[15,82,83]

While phytosomes enhance poorly soluble phytochemical absorption, achieving uniform particle size and stability requires advanced formulation techniques. Kattyar et al. demonstrated improved solubility and gastrointestinal absorption of Vasicine phytosomes for asthma treatment. These studies emphasize the need for optimized phospholipid complexation and co-processing techniques to maximize herbal bioactive efficacy.[84]

4.5. Skin sensitivity and irritation potential

Although phytosomal gels are biocompatible, they may cause skin irritation or sensitization, particularly in sensitive individuals. Lipid components and herbal actives can trigger allergic reactions, requiring pH optimization and irritation testing.[74] Dwivedi et al. highlighted advances in phytosome nanotechnology for curcumin and silymarin absorption but noted limited penetration and skin sensitivity issues. Similarly, Damle & Mallya developed a polyherbal phospholipid cream with improved skin retention and antioxidant effects, though its phospholipids and polyphenols required irritation assessments.[55,85]

Minimizing skin irritation risks is essential for safe phytosomal gel formulation. Nashaat et al. demonstrated CUR/LEF-loaded phytosomes improved anti-inflammatory effects in rheumatoid arthritis but emphasized safety evaluations. Leanpolchareanchai & Teeranachaideekul reviewed microemulsions for herbal bioactives, raising concerns about surfactant-induced irritation. These findings stress the need for dermatological testing and skin-friendly excipients to ensure safe and effective phytosomal gels.[86,87]

4.6. Standardization of herbal extracts

Ensuring herbal extract consistency in phytosomal formulations is challenging due to natural variability in phytochemical composition, affecting potency and bioavailability.[88] Angadi et al. formulated a Moringa oleifera phytosome, improving antioxidant activity but stressing the need for precise extraction and characterization. Similarly, Laxman Thakur & Sabanna Patil developed a Tinospora cordifolia alkaloid-loaded phytosome, emphasizing controlled extraction and fractionation to enhance bioavailability.[89,90]

Achieving batch-to-batch consistency requires advanced analytics and process optimization. Researcher developed a stable curcumin phytosomal gel with long-term stability and enhanced absorption, underscoring the need for meticulous formulation control. These studies highlight the importance of standardized extraction, characterization, and validation to ensure consistent therapeutic efficacy in phytosomal formulations.

4.7. Regulatory and quality control issues

Phytosomal gels with herbal extracts face regulatory and quality control challenges due to global variations in safety, efficacy, and quality standards.[91] Compliance with stringent regulations is costly and time-consuming, limiting market accessibility. Sumant et al. emphasized Quality-by-Design (QbD) principles, integrating risk management and in-process quality control for standardized formulations. Pavithra & Manimaran stressed adherence to WHO guidelines and Good Agricultural and Collection Practices (GACP) to ensure quality and clinical success in phytopharmaceuticals.[91,92]

Ensuring bioavailability and stability is key to regulatory compliance. Adewale noted rising consumer demand for natural skincare, emphasizing regulatory certifications like halal and sustainable extraction for industry compliance. Addressing these challenges requires rigorous quality control, regulatory adherence, and innovative formulations to enhance phytosomal product viability.[93]

4.8. Formulation scalability

Scaling up phytosomal gel production from laboratory to commercial levels presents technical challenges, requiring precise control over particle size, dispersion stability, and phytosome integrity, which can be resource-intensive. Investigator emphasized that phytosome-based formulations enhance bioavailability and efficacy, they demand advanced manufacturing techniques for consistency. Similarly, Allaw et al. highlighted the need for efficient and eco-friendly

formulation strategies to improve scalability and clinical application of plant-derived bioactives.[94]

Limited solubility and bioavailability of some phytochemicals also impact large-scale formulation stability. Tallam et al. discussed nano-vesicular systems such as pyrosomes, improving phytochemical bioavailability and emphasizing the need for commercial translation of laboratory-scale innovations. Overcoming these challenges requires optimized formulation techniques, scalable manufacturing, and strict quality control to ensure consistent and effective commercial phytosomal gels.[95]

5. Future Directions and Research Opportunities in Herbal Phytosomal Gel Formulation

5.1. Advancements in stabilization techniques

Improving phytosomal gel stability with novel stabilizers, antioxidant agents, and protective packaging can enhance shelf-life. Nanotechnology-based approaches, such as nanoencapsulation, may further stabilize delivery systems.[96]

5.2. Cost-effective phospholipid sources

Identifying affordable phospholipids or alternative natural lipids can improve cost-efficiency. Advances in synthetic or plant-derived phospholipids may enhance availability and sustainability for large-scale production.[97]

5.3. Enhanced bioavailability strategies

Optimizing phospholipid-herbal active ratios and exploring hybrid systems (e.g., liposomes, solid lipid nanoparticles) could improve bioavailability, skin penetration, and controlled release.[98]

5.4. Multifunctional phytosomal gels

Combining complementary herbal extracts in one formulation can create gels with multiple benefits, such as anti-aging, hydration, and skin brightening, catering to consumer demand.

5.5. Standardization & quality control

Advanced techniques like HPLC and mass spectrometry can improve batch-to-batch consistency, ensuring potency and efficacy in phytosomal formulations.[88]

5.6. Expanded applications beyond skincare

Phytosomal gels could be developed for transdermal applications, delivering therapeutic compounds for joint pain, inflammation, or infections, broadening their medical use.[99]

5.7. Clinical validation

More in vivo and clinical trials are needed to establish efficacy, optimal dosing, and safety, ensuring regulatory approval and consumer confidence. Sustainability & Green Chemistry: Eco-friendly extraction, solvent-free processing, and biodegradable packaging can enhance sustainability, aligning with consumer and industry trends.[100]

5.8. Regulatory & global standards

Harmonizing formulation, testing, and labeling standards can streamline global regulatory approval, ensuring safety and market accessibility.[91]

6. Conclusion

Herbal phytosomal gels represent a promising advancement in the field of drug delivery, merging traditional herbal medicine with modern pharmaceutical technology. By enhancing the solubility, stability, and bioavailability of bioactive compounds through phospholipid complexation, these formulations offer significant therapeutic potential for various applications, including anti-inflammatory treatments, wound healing, and skincare. However, challenges such as stability issues, high production costs, and regulatory hurdles must be addressed to facilitate their widespread adoption. Future research should focus on optimizing formulation techniques, exploring cost-effective phospholipid sources, and ensuring rigorous quality control to enhance the efficacy and safety of phytosomal gels. Additionally, expanding their applications beyond skincare and validating their benefits through clinical trials will be crucial for gaining consumer trust and regulatory approval. As the demand for natural remedies continues to rise, the integration of phytosomal technology into herbal formulations could pave the way for innovative therapeutic solutions, ultimately improving patient outcomes and promoting holistic health. By overcoming existing challenges and leveraging advancements in formulation science, herbal phytosomal gels have the potential to revolutionize the landscape of herbal medicine and cosmetic applications.

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8. Conflict of Interest

None.

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