RECENT ADVANCES IN PHYTOSOMAL DRUG DELIVERY SYSTEMS FOR TOPICAL APPLICATIONS

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Abstract

Phytosomal drug delivery systems are advanced lipid-based carriers developed to improve the topical delivery of plant-derived bioactive compounds. Conventional herbal formulations often suffer from poor solubility, low bioavailability, chemical instability, and limited skin penetration, which reduce their therapeutic effectiveness. Phytosomes overcome these limitations by forming molecular complexes between phytochemicals and phospholipids, particularly phosphatidylcholine, resulting in enhanced stability, membrane permeability, and controlled release. This review summarizes recent developments in phytosomal systems for topical and transdermal applications. It discusses major preparation techniques, including solvent evaporation, anti-solvent precipitation, and supercritical fluid methods, along with important characterization approaches such as spectroscopic, thermal, and microscopic analysis. The review also highlights the mechanisms responsible for improved skin penetration and enhanced dermal absorption. Therapeutic and cosmetic applications of phytosomes in anti-ageing, wound healing, inflammatory skin disorders, antimicrobial therapy, and photoprotection are critically discussed. Despite significant progress, challenges related to herbal standardization, large-scale manufacturing, regulatory approval, and limited clinical studies remain. Phytosomal technology represents a promising strategy for enhancing the efficacy and topical performance of phytochemicals in dermatological and cosmeceutical formulations.

Keywords: *Phytosomes, topical drug delivery, phospholipids, phytochemicals, skin permeation, nanocarriers, herbal formulations, Dermatology, transdermal delivery*

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Received: 23/05/2026
Revised: 23/07/2026
Accepted: 31/07/2026
DOI: http://doi.org/10.66204/GJPSR-1170-2026-2-8-1

How to Cite

Singh A, Yadav VK, Agrahari H. Recent Advances in Phytosomal Drug Delivery Systems for Topical Applications. Global Journal of Pharmaceutical and Scientific Research. 2026;2(8):1170-1186. ISSN: 3108-0103. http://doi.org/10.66204/GJPSR-1170-2026-2-8-1.

1. INTRODUCTION

1.1 Background and Rationale

Medicinal plants and their bioactive phytoconstituents have gained considerable attention owing to their antioxidant, anti-inflammatory, antimicrobial, anticancer, and wound-healing properties. However, the therapeutic potential of many phytochemicals, including curcumin, quercetin, silymarin, and resveratrol, is often limited by poor aqueous solubility, low membrane permeability, chemical instability, and inadequate bioavailability. These limitations reduce their clinical efficacy and hinder their successful incorporation into conventional topical dosage forms (Talebi et al., 2025; Raghav et al., 2025).

Topical drug delivery provides localized therapeutic action, minimizes systemic adverse effects, and improves patient compliance. Nevertheless, the highly organized structure of the stratum corneum acts as the principal barrier to drug permeation, restricting the penetration and retention of many phytoconstituents within the skin. Consequently, conventional creams, ointments, and gels often fail to achieve sufficient drug concentrations at the target site, thereby limiting their therapeutic effectiveness (Nemade et al., 2025; Mandwe et al., 2025).

To overcome these challenges, phytosomes have emerged as an advanced phospholipid-based drug delivery system in which phytoconstituents form stable molecular complexes with phospholipids, primarily phosphatidylcholine. Unlike conventional liposomes, phytosomes enhance the lipid compatibility of phytochemicals, resulting in improved skin permeation, physicochemical stability, controlled drug release, and enhanced bioavailability. These advantages have positioned phytosomes as one of the most promising nanocarriers for topical delivery of herbal bioactives (Talebi et al., 2025; Deniz et al., 2025).

Recent developments in phytosomal technology, including nano-phytosomes, surface-functionalized phytosomes, and hybrid lipid nanocarriers, have further expanded their applications in wound healing, inflammatory skin disorders, fungal infections, acne, psoriasis, and cosmetic dermatology. These advances highlight the growing importance of phytosomal drug delivery systems in improving the therapeutic performance of plant-derived compounds for topical applications (Purohit & Mishra, 2025; Talebi et al., 2025).

1.2 Evolution of Phytosome Technology

The concept of phytosome technology was introduced in the late 1980s by the Italian pharmaceutical company **Indena S.p.A.** to improve the absorption and therapeutic efficacy of plant-derived bioactive compounds. The technology involves the formation of a molecular complex between phytoconstituents and phospholipids, particularly phosphatidylcholine,

through hydrogen bonding. Unlike conventional liposomes, where the active compound is physically entrapped, phytosomes chemically bind the phytoconstituent to the phospholipid, resulting in improved stability, membrane permeability, and bioavailability (Bombardelli et al., 1989; Talebi et al., 2025).

Initially, phytosome technology was developed to enhance the oral bioavailability of poorly absorbed herbal extracts such as **silymarin, Ginkgo biloba, grape seed extract, green tea polyphenols, and curcumin**. Encouraging pharmacokinetic and therapeutic outcomes subsequently expanded its application to various drug delivery routes, including topical, transdermal, ocular, and nasal administration (Semalty et al., 2007; Deniz et al., 2025).

Recent advancements have significantly transformed phytosome technology through the development of **nano-phytosomes**, **surface-functionalized phytosomes**, and **hybrid lipid-based nanocarriers**, which provide enhanced encapsulation efficiency, controlled drug release, improved skin permeation, and targeted delivery. These innovations have accelerated the application of phytosomal formulations in the treatment of wound healing, inflammatory skin diseases, fungal infections, psoriasis, acne, and cosmetic dermatology, making phytosomes one of the most promising lipid-based nanocarrier systems for topical drug delivery (Talebi et al., 2025; Purohit & Mishra, 2025).

1.3 Scope and Objectives

The growing interest in plant-based therapeutics and nanotechnology has positioned phytosomal drug delivery systems as a promising strategy for enhancing the topical delivery of phytoconstituents. Phytosomes improve the physicochemical properties, skin permeation, stability, and therapeutic efficacy of herbal bioactive compounds, making them suitable for the management of various dermatological disorders. Recent advancements, including nano-phytosomes and surface-modified phytosomes, have further broadened their pharmaceutical and cosmeceutical applications (Talebi et al., 2025; Deniz et al., 2025).

This review aims to provide a comprehensive overview of recent advances in phytosomal drug delivery systems for topical applications. It discusses the principles of phytosome technology, formulation approaches, preparation methods, characterization techniques, mechanisms of skin permeation, therapeutic applications, recent innovations, commercially available products, regulatory considerations, and future prospects. The review also highlights current challenges and emerging opportunities for translating phytosomal formulations into clinically effective topical therapies (Raghav et al., 2025; Purohit & Mishra, 2025).

2. Fundamental Principles of Phytosome Technology

2.1 Structural Architecture and Molecular Organization

Phytosomes are advanced lipid-based nanocarriers formed by the complexation of phytoconstituents with phospholipids, predominantly **phosphatidylcholine (PC)**, in a defined molar ratio (commonly 1:1 or 1:2). The complex is stabilized through hydrogen bonding and hydrophobic interactions between the polar functional groups of the phytoconstituent (e.g., hydroxyl or carboxyl groups) and the polar head of phosphatidylcholine. This molecular interaction distinguishes phytosomes from conventional liposomes, where the active compound is only physically entrapped within the phospholipid bilayer (Semalty et al., 2007; Talebi et al., 2025).

Structurally, a phytosome consists of a phytochemical-phospholipid molecular complex in which the hydrophilic phytoconstituent is chemically associated with the polar head of phosphatidylcholine, while the lipophilic fatty acid tails remain oriented outward. This amphiphilic organization enhances the lipid compatibility of phytochemicals, improves membrane affinity, and facilitates their penetration through biological membranes, particularly the stratum corneum of the skin. As a result, phytosomes exhibit superior stability, enhanced skin permeation, and improved therapeutic efficacy compared with conventional herbal formulations (Deniz et al., 2025; Raghav et al., 2025).

2.2 Phospholipid Chemistry and Selection

Phospholipids are the principal structural components of phytosomes and play a crucial role in improving the delivery of phytoconstituents. The most widely used phospholipid is phosphatidylcholine (PC), a naturally occurring amphiphilic molecule composed of a hydrophilic phosphate-choline head and two hydrophobic fatty acid tails. This unique structure enables phosphatidylcholine to form stable molecular complexes with phytochemicals through hydrogen bonding, thereby enhancing their lipophilicity, membrane permeability, and physicochemical stability (Semalty et al., 2007; Talebi et al., 2025).

The selection of phospholipids depends on their purity, fatty acid composition, biocompatibility, and compatibility with the phytoconstituent. Soybean-derived phosphatidylcholine is the most commonly employed phospholipid because of its high phosphatidylcholine content, biodegradability, low toxicity, and excellent complex-forming ability. Other phospholipids, including hydrogenated phosphatidylcholine (HPC), phosphatidylethanolamine (PE), and phosphatidylserine (PS), are also used to improve the stability, rigidity, and drug-loading capacity of phytosomal formulations for specific therapeutic applications (Deniz et al., 2025; Raghav et al., 2025).

The phospholipid-to-phytoconstituent ratio is another critical parameter influencing phytosome performance. Ratios of 1:1 or 1:2 (molar ratio) are commonly employed to achieve stable complex formation, high encapsulation efficiency, and enhanced skin permeation. Appropriate phospholipid selection and optimization contribute significantly to improved drug release, prolonged skin retention, and enhanced therapeutic efficacy in topical drug delivery systems (Talebi et al., 2025; Purohit & Mishra, 2025).

2.3 Thermodynamic and Kinetic Considerations

The formation of phytosomes is governed by thermodynamic and kinetic principles that promote the spontaneous complexation of phytoconstituents with phospholipids. The interaction is primarily driven by **hydrogen bonding**, **van der Waals forces**, and **hydrophobic interactions** between the polar functional groups of phytochemicals (e.g., hydroxyl and carboxyl groups) and the polar head of phosphatidylcholine. These non-covalent interactions result in the formation of a thermodynamically stable molecular complex with enhanced physicochemical stability and reduced free energy (Semalty et al., 2007; Talebi et al., 2025).

The stability and performance of phytosomes are influenced by several kinetic factors, including the phospholipid-to-phytoconstituent ratio, solvent system, temperature, mixing conditions, and preparation method. Optimizing these parameters improves complexation efficiency, particle size distribution, encapsulation efficiency, and long-term stability while minimizing aggregation. Such optimization is essential for achieving reproducible formulations with enhanced skin permeation and sustained therapeutic performance in topical applications (Deniz et al., 2025; Raghav et al., 2025).

3. Preparation Methods and Formulation Strategies

3.1 Solvent Evaporation Method

The **solvent evaporation method** is one of the most widely employed techniques for preparing phytosomes due to its simplicity, reproducibility, and high complexation efficiency. In this method, the phytoconstituent and phospholipid (commonly phosphatidylcholine) are dissolved in a suitable organic solvent such as **ethanol, methanol, dichloromethane, or acetone** at a predetermined molar ratio (typically 1:1 or 1:2). The resulting solution is refluxed or stirred at a controlled temperature to facilitate the formation of a stable phytoconstituent-phospholipid complex through hydrogen bonding (Semalty et al., 2007; Talebi et al., 2025).

Following complex formation, the organic solvent is removed under reduced pressure using a **rotary evaporator**, resulting in a thin film or dry phytosomal complex. The dried complex is

subsequently collected, vacuum-dried to eliminate residual solvent, and stored under appropriate conditions. The solvent evaporation method produces phytosomes with high encapsulation efficiency, uniform particle size, enhanced stability, and improved bioavailability, making it suitable for both laboratory-scale and industrial-scale production (Deniz et al., 2025; Raghav et al., 2025).

3.2 Anti-Solvent Precipitation Method

The **anti-solvent precipitation method** is an effective technique for preparing phytosomes, particularly for phytoconstituents with limited solubility in conventional organic solvents. In this method, the phytochemical and phospholipid are first dissolved in a suitable solvent such as ethanol or methanol, and the resulting solution is slowly added to a large volume of anti-solvent under continuous stirring. The rapid decrease in solubility induces supersaturation, leading to the precipitation of stable phyto-phospholipid complexes with relatively uniform particle size (Semalty et al., 2007; Talebi et al., 2025).

Critical process parameters, including the solvent-to-antisolvent ratio, addition rate, stirring speed, and temperature, markedly influence particle size, encapsulation efficiency, morphology, and production yield. The precipitated phytosomes are subsequently collected by filtration or centrifugation, washed to remove unbound components, and dried under controlled conditions. Compared with the solvent evaporation method, the anti-solvent precipitation technique generally produces smaller particles with a larger surface area, thereby enhancing skin permeation and improving the therapeutic performance of topical phytosomal formulations (Deniz et al., 2025; Raghav et al., 2025).

3.3 Supercritical Fluid Technology

Supercritical fluid (SCF) technology is an advanced and environmentally friendly approach for the preparation of phytosomes, offering precise control over particle size and morphology while minimizing the use of organic solvents. In this method, supercritical carbon dioxide (SC-CO_2) is commonly employed because of its non-toxic, non-flammable, and easily removable nature. The phytochemical and phospholipid are dissolved in a suitable solvent and processed under supercritical conditions, where rapid expansion or solvent extraction facilitates the formation of fine phytosomal particles (Talebi et al., 2025; Deniz et al., 2025).

Phytosomes produced using SCF technology generally exhibit uniform particle size, high encapsulation efficiency, improved stability, and minimal residual solvent content. Process variables such as pressure, temperature, and flow rate significantly influence particle characteristics and formulation performance. Owing to these advantages, SCF technology has emerged as a promising technique for developing high-quality phytosomal formulations with

enhanced topical drug delivery, although its industrial application remains limited by high equipment costs and operational complexity (Semalty et al., 2007; Raghav et al., 2025).

3.4 Quality by Design (QbD) Approaches

Quality by Design (QbD) is a systematic, science- and risk-based approach to pharmaceutical development that emphasizes building quality into a product from the initial stages rather than relying solely on end-product testing. In phytosomal formulation development, QbD facilitates a thorough understanding of the relationship between formulation variables and product performance, ensuring consistent quality, safety, and efficacy (ICH Q8(R2); Talebi et al., 2025).

The QbD framework begins with the establishment of a Quality Target Product Profile (QTPP), followed by the identification of Critical Quality Attributes (CQAs) such as particle size, polydispersity index, zeta potential, encapsulation efficiency, and drug release. Critical Material Attributes (CMAs), including phospholipid type, phytochemical-to-phospholipid ratio, and solvent selection, together with Critical Process Parameters (CPPs) such as temperature, stirring speed, and mixing time, are systematically optimized using Design of Experiments (DoE). This approach improves process robustness, enhances reproducibility, and facilitates scale-up and regulatory compliance (Yu, 2008; ICH Q8(R2); Deniz et al., 2025).

The application of QbD has significantly improved the development of phytosomal formulations by reducing formulation variability, increasing encapsulation efficiency, optimizing skin permeation, and accelerating product development. Consequently, QbD has become an important strategy for the successful translation of phytosomal drug delivery systems from laboratory research to industrial manufacturing (Talebi et al., 2025; Raghav et al., 2025).

4. Characterization Techniques

4.1 Spectroscopic Analysis

Spectroscopic techniques are widely employed to confirm the formation of phytosome complexes and to evaluate molecular interactions between phytoconstituents and phospholipids. Fourier Transform Infrared Spectroscopy (FTIR) is the most commonly used method to identify hydrogen bonding and functional group interactions by detecting shifts in characteristic absorption peaks. Nuclear Magnetic Resonance (NMR) spectroscopy provides structural information regarding the molecular arrangement and confirms the successful complexation of phytochemicals with phospholipids. Additionally, UV-Visible spectroscopy

is used to determine drug content and assess the stability of phytosomal formulations (Semalty et al., 2007; Talebi et al., 2025).

4.2 Microscopic and Morphological Characterization

Microscopic analysis is performed to evaluate the morphology, surface characteristics, and internal structure of phytosomes. Scanning Electron Microscopy (SEM) provides information on particle shape and surface morphology, whereas Transmission Electron Microscopy (TEM) reveals vesicle size, internal architecture, and lamellar organization at the nanoscale. Atomic Force Microscopy (AFM) may also be employed to assess surface topography and particle roughness. These techniques confirm the successful formation of phytosomes and ensure uniformity of the formulation (Talebi et al., 2025; Raghav et al., 2025).

4.3 Thermal Analysis

Thermal characterization is essential for evaluating the physical state, compatibility, and thermal stability of phytosomal formulations. Differential Scanning Calorimetry (DSC) is commonly used to detect changes in melting behavior, indicating successful complex formation between phytoconstituents and phospholipids. Thermogravimetric Analysis (TGA) measures weight loss with increasing temperature to assess thermal degradation and moisture content, while X-ray Diffraction (XRD) complements thermal analysis by determining the crystalline or amorphous nature of the phytosome complex (Semalty et al., 2007; Deniz et al., 2025).

4.4 Particle Size and Surface Charge Analysis

Particle size and surface charge are critical parameters influencing the stability, skin permeation, and therapeutic performance of phytosomes. Dynamic Light Scattering (DLS) is routinely used to determine particle size and polydispersity index (PDI), which reflects the uniformity of particle distribution. Zeta potential analysis evaluates the surface charge of phytosomes and predicts colloidal stability, with higher absolute zeta potential values generally indicating greater resistance to aggregation. Optimizing these parameters contributes to enhanced encapsulation efficiency, prolonged stability, and improved topical drug delivery (Talebi et al., 2025; Raghav et al., 2025).

5. Mechanisms of Enhanced Topical Delivery

5.1 Stratum Corneum Penetration Mechanisms

The stratum corneum is the primary barrier to topical drug delivery, limiting the penetration of many hydrophilic phytoconstituents. Phytosomes enhance skin permeation by increasing the lipophilicity of phytochemicals through complexation with phospholipids, particularly phosphatidylcholine. This amphiphilic complex exhibits greater affinity for the lipid matrix

of the stratum corneum, facilitating diffusion through the intercellular lipid pathway. Furthermore, the phospholipid component interacts with skin lipids, improving drug partitioning, retention, and controlled release within deeper skin layers, thereby enhancing topical bioavailability (Semalty et al., 2007; Talebi et al., 2025).

5.2 Cellular Uptake and Intracellular Delivery

The nanoscale size and lipidic nature of phytosomes facilitate efficient uptake by skin cells through endocytosis and membrane fusion. Following penetration across the stratum corneum, phytosomal complexes are internalized by keratinocytes and fibroblasts, enabling intracellular release of phytoconstituents. This enhanced cellular uptake improves the local concentration of bioactive compounds, leading to greater antioxidant, anti-inflammatory, antimicrobial, and wound-healing activities compared with conventional topical formulations (Deniz et al., 2025; Talebi et al., 2025).

5.3 Protection from Enzymatic and Chemical Degradation

Phytoconstituents are susceptible to oxidation, hydrolysis, photodegradation, and enzymatic degradation, which can reduce their therapeutic efficacy. Complexation with phospholipids forms a protective molecular envelope around the phytochemical, shielding it from external environmental factors and metabolic enzymes. This protective effect improves chemical stability, prolongs drug residence time within the skin, and enables sustained release, ultimately enhancing the therapeutic performance of topical phytosomal formulations (Talebi et al., 2025; Raghav et al., 2025).

6. Therapeutic Applications in Dermatology

6.1 Anti-Ageing and Photoprotection

Phytosomal formulations have shown significant potential in anti-ageing and photoprotective skincare by enhancing the dermal delivery of natural antioxidants such as curcumin, resveratrol, quercetin, and green tea polyphenols. These phytoconstituents effectively neutralize reactive oxygen species (ROS), inhibit collagen degradation, suppress matrix metalloproteinase (MMP) activity, and reduce UV-induced oxidative stress, thereby preventing premature skin ageing, wrinkle formation, and photoaging. Phytosomal encapsulation further improves skin penetration, stability, and prolonged retention of these bioactive compounds, resulting in enhanced photoprotective efficacy compared with conventional formulations (Hecker et al., 2022; Barani et al., 2021; Mo et al., 2024).

6.2 Inflammatory Skin Disorders

Phytosomes have been extensively investigated for the treatment of inflammatory skin disorders such as psoriasis, eczema, atopic dermatitis, and acne vulgaris. Encapsulation of phytochemicals including curcumin, boswellic acid, quercetin, apigenin, and resveratrol enhances their penetration into inflamed skin and improves local drug retention. These compounds suppress the production of pro-inflammatory cytokines, reduce oxidative stress, and inhibit NF-κB, MAPK, and COX-2 signaling pathways, leading to improved therapeutic outcomes with reduced systemic adverse effects. Clinical evidence has also demonstrated that quercetin phytosomes effectively reduce UV-induced erythema and improve skin hydration, highlighting their therapeutic value in inflammatory dermatological conditions (Barani et al., 2021; Mo et al., 2024; Hecker et al., 2022).

6.3 Wound Healing and Tissue Regeneration

Phytosomal drug delivery systems have demonstrated promising results in accelerating wound healing and tissue regeneration by improving the topical delivery of bioactive compounds such as curcumin, **Centella asiatica**, Aloe vera, quercetin, and Calendula officinalis. Enhanced skin permeation and sustained release promote collagen synthesis, angiogenesis, fibroblast proliferation, extracellular matrix remodeling, and re-epithelialization while reducing oxidative stress and inflammation. Consequently, phytosomal formulations facilitate faster wound closure and improved tissue repair compared with conventional topical preparations (Hecker et al., 2022; Barani et al., 2021; Zhang et al., 2022).

6.4 Antimicrobial Applications

Phytosomal formulations have emerged as effective carriers for delivering antimicrobial phytochemicals against bacterial and fungal skin infections. Bioactive compounds such as berberine, neem extract, tea tree oil, garlic extract, curcumin, and green tea catechins exhibit enhanced antimicrobial activity when formulated as phytosomes due to improved skin penetration, sustained release, and increased retention at the infection site. These formulations have shown promising efficacy against pathogens including Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa, and Candida albicans, while simultaneously reducing inflammation and promoting wound repair. Such multifunctional properties make phytosomal systems promising alternatives for managing superficial skin infections and reducing dependence on conventional antibiotics (Mo et al., 2024; Barani et al., 2021; Zhang et al., 2022).

7. Cosmetic and Cosmeceutical Applications

7.1 Skin Brightening and Anti-Pigmentation

Phytosomal technology has gained considerable attention in cosmeceutical formulations for the management of hyperpigmentation and uneven skin tone. Bioactive compounds such as **glabridin, arbutin, licorice extract, resveratrol, green tea polyphenols, and vitamin C** inhibit tyrosinase activity, suppress melanogenesis, and reduce oxidative stress associated with UV-induced pigmentation. Phytosomal encapsulation enhances the stability, skin permeation, and dermal retention of these phytoconstituents, thereby improving their depigmenting efficacy and photoprotective effects compared with conventional topical formulations (Yahya et al., 2021; Chan et al., 2024).

7.2 Moisturizing and Barrier Repair

Phytosomal formulations enhance skin hydration and restore epidermal barrier integrity by improving the delivery of moisturizing and antioxidant phytochemicals. Extracts of Aloe vera, Centella asiatica, Calendula officinalis, and Camellia sinensis have demonstrated the ability to reduce transepidermal water loss (TEWL), promote collagen synthesis, and accelerate skin repair. Complexation with phospholipids increases the penetration and retention of these bioactives within the epidermis, resulting in prolonged hydration and improved barrier function (Yahya et al., 2021; Chan et al., 2024).

7.3 Anti-Cellulite and Body Contouring

Phytosomes have emerged as promising carriers for anti-cellulite and body contouring formulations because they improve the dermal delivery of lipolytic and microcirculation-enhancing phytochemicals. Active compounds such as **caffeine, green tea catechins, Centella asiatica, horse chestnut extract, and grape seed polyphenols** enhance local blood circulation, stimulate lipid metabolism, and reduce fluid accumulation in subcutaneous tissues. Phytosomal encapsulation increases the bioavailability and sustained release of these compounds, thereby improving skin firmness and reducing the appearance of cellulite (Kapse & Mulla, 2024; Kalaivani & Kamaraj, 2024).

Table 8.1. Currently Marketed Phytosome® Products

Product (Trademark)	**Active Phytoconstituent**	**Botanical Source**	**Major Application**	**Manufacturer**
Meriva®	Curcumin Phytosome	*Curcuma longa*	Anti-inflammatory,	Indena S.p.A.

			joint health, skin health	
Quercefit®	Quercetin Phytosome	*Sophora japonica*	Antioxidant, anti-ageing, skin health	Indena S.p.A.
Greenselect® Phytosome	Green Tea Polyphenols (EGCG)	*Camellia sinensis*	Antioxidant, weight management, photoprotection	Indena S.p.A.
Leucoselect® Phytosome	Grape Seed Proanthocyanidins	*Vitis vinifera*	Antioxidant, UV protection, vascular health	Indena S.p.A.
Siliphos®	Silybin Phytosome	*Silybum marianum*	Hepatoprotection, antioxidant activity	Indena S.p.A.
Silymarin Indena Phytosome®	Silymarin	*Silybum marianum*	Liver health, antioxidant, UV protection	Indena S.p.A.
Casperome®	Boswellic Acids Phytosome	*Boswellia serrata*	Anti-inflammatory, musculoskeletal disorders	Indena S.p.A.
Berbevis®	Berberine Phytosome	*Berberis aristata*	Metabolic health, skin health	Indena S.p.A.
Ubiqsome®	Coenzyme Q10 Phytosome	Coenzyme Q10	Anti-ageing, skin health, cellular energy	Indena S.p.A.
Ginkgoselect® Plus	Ginkgo biloba	*Ginkgo*	Cognitive function,	Indena

Phytosome	Extract	*biloba*	antioxidant, microcirculation	S.p.A.
Vazguard®	Bergamot Flavonoids Phytosome	*Citrus bergamia*	Cardiovascular and metabolic health	Indena S.p.A.
Centextra®	Centella asiatica Phytosome	*Centella asiatica*	Skin repair, wound healing, healthy ageing	Indena S.p.A.
Relissa®	Melissa officinalis Phytosome	*Melissa officinalis*	Stress reduction, relaxation, sleep support	Indena S.p.A.
Anthocran® Phytosome	Cranberry Extract	*Vaccinium macrocarpon*	Urinary tract health, antioxidant	Indena S.p.A.

9. Challenges and Future Directions

9.1 Current Limitations

Despite their promising therapeutic potential, phytosomal drug delivery systems still face several challenges that limit their widespread clinical and commercial application. Phospholipid oxidation, hydrolysis, and drug leakage during storage can compromise formulation stability and reduce shelf life. Moreover, maintaining consistent particle size, encapsulation efficiency, and batch-to-batch reproducibility during large-scale manufacturing remains technically demanding. The requirement for high-purity phospholipids, sophisticated manufacturing processes, and specialized analytical techniques further increases production costs. In addition, limited clinical evidence, inadequate long-term safety data, and the absence of harmonized regulatory guidelines for herbal nanocarriers continue to delay the translation of phytosomal formulations into commercially approved topical products (Barani et al., 2021; Pandey et al., 2024; Mandwe et al., 2025).

9.2 Emerging Innovations

Recent advances in nanotechnology are expanding the therapeutic potential of phytosomal drug delivery systems. Emerging strategies, including nano-phytosomes, ligand-targeted phytosomes, PEGylated systems, and hybrid lipid nanocarriers, have demonstrated improved encapsulation efficiency, controlled drug release, and enhanced skin penetration. The implementation of Quality by Design (QbD) and Design of Experiments (DoE) has enabled systematic optimization of formulation variables, improving product quality and manufacturing reproducibility. Furthermore, the integration of phytosomes with advanced topical platforms such as microneedle arrays, hydrogels, emulgels, and 3D-printed dosage forms is expected to enhance localized drug delivery and patient compliance. Future progress will depend on well-designed clinical studies, scalable manufacturing technologies, and the establishment of standardized regulatory frameworks to facilitate successful commercialization (Kapse & Mulla, 2024; Raghav et al., 2024; Alkilani et al., 2024).

10. Conclusion

Phytosomal drug delivery systems have emerged as an effective strategy for improving the topical delivery of plant-derived bioactive compounds by overcoming challenges such as poor solubility, low bioavailability, and limited skin permeation. Through molecular complexation with phospholipids, phytosomes enhance the stability, membrane compatibility, and therapeutic performance of phytochemicals, making them more suitable for dermatological and cosmetic applications. Their ability to improve penetration across the stratum corneum and facilitate sustained release has contributed to better outcomes in conditions related to skin ageing, inflammation, wound healing, pigmentation disorders, and microbial infections.

Over the past few years, substantial progress has been made in formulation approaches, characterization techniques, and mechanistic understanding of phytosomal systems. Increasing commercial interest and the availability of phytosome-based products further highlight the practical relevance of this technology in both pharmaceutical and cosmeceutical sectors. Nevertheless, issues related to extract standardization, large-scale production, regulatory approval, and long-term clinical validation still require careful attention.

Future research should focus on well-designed clinical studies, development of cost-effective manufacturing processes, and integration of advanced delivery approaches such as hybrid nanocarriers and stimuli-responsive systems. Overall, phytosomal technology offers a promising bridge between traditional herbal therapeutics and modern drug delivery science,

with strong potential for the development of safer, more efficient, and patient-friendly topical formulations.

11. Acknowledgements

The authors would like to express their sincere gratitude to all the researchers and institutions whose work has contributed to the development of this review.

12. Conflict of Interest

The authors declare that there are no conflicts of interest regarding the publication of this review.

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