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Review Article

Phytosome: Unlocking the Therapeutic Potential of Herbal Phytoconstituents

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ABSTRACT

Herbal medicines are widely used across the world due to their safety, cultural acceptance, and significant therapeutic potential. However, poor bioavailability remains a major limitation for many phytoconstituents. Most plant-derived active compounds, including flavonoids, glycosides, polyphenols, tannins, and alkaloids, exhibit low absorption and reduced systemic availability because of their large molecular size, poor lipid solubility, and limited membrane permeability. As a result, higher doses are often required to achieve therapeutic effects, which may reduce patient compliance. Phytosome technology has emerged as an advanced drug delivery system designed to overcome these challenges by complexing phytoconstituents with phospholipids, thereby improving their compatibility with biological membranes. The formation of a phospholipid–phytoconstituent complex enhances absorption, increases bioavailability, improves stability, and prolongs therapeutic activity. This review highlights the fundamental concept of phytosomes, various preparation methods, characterization techniques, advantages, limitations, and diverse applications in herbal drug delivery. Additionally, recent advancements and commercially available phytosomal formulations are discussed to emphasize their growing significance in modern phytopharmaceutical research.

INTRODUCTION

Herbal drug products have gained significant attention due to their potential therapeutic benefits and minimal side effects compared to conventional synthetic drugs. However, the bioavailability of these herbal compounds is often limited due to their poor solubility and absorption. Phytosomes, a novel drug delivery system, have emerged as a promising solution to these challenges by enhancing the bioavailability and therapeutic efficacy of herbal drugs. This innovative approach involves the encapsulation of herbal extracts with phospholipids, forming complexes that improve solubility and absorption. The importance of

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phytosomes in herbal drug formulation can be understood through several key aspects.

a. Enhanced Bioavailability and Solubility

- Phytosomes improve the solubility and bioavailability of herbal compounds, which are typically lipid-insoluble, by forming lipid-compatible molecular complexes with phospholipids like phosphatidylcholine[1,2]
- This technology allows for better absorption of active phytoconstituents, such as flavonoids and terpenoids, across biological membranes [3]

b. Therapeutic Efficacy and Applications

- Phytosomes have been shown to enhance the therapeutic efficacy of herbal drugs, allowing for lower therapeutic doses and targeted delivery [4]
- They are used in various applications, including dietary supplements and cosmetics, and have been effective in managing conditions like inflammation, cancer, and heart disease[1,2]

c. Advancements and Market Presence

- Recent advancements in phytosome technology have led to the development of transdermal delivery systems, further expanding their application [3]
- Several phytosomal products, such as those containing curcumin and silymarin, are already available in the market, demonstrating their commercial viability [5]

While phytosomes offer significant advantages in herbal drug delivery, challenges remain in standardizing quality control methods and ensuring consistent production. Further research and development in this area could enhance the reliability and effectiveness of phytosomal formulations, potentially revolutionizing the field of herbal medicine delivery systems.

2. CONCEPT OF PHYTOSOME

Phytosomes are innovative lipid-based nanovesicles in which standardized plant extracts or isolated polyphenolic phytochemicals are molecularly complexed with phospholipids, predominantly phosphatidylcholine, through hydrogen bonding between the polyphenolic moieties and the phosphate–choline head group. This interaction produces self-assembled vesicular systems structurally related to liposomes, encapsulating active phytoconstituents within a lipid environment and thereby overcoming the intrinsic hydrophilicity and membrane-permeation barriers of many glycosides and flavonoids. By improving compatibility with lipid-rich biological membranes, phytosomes markedly enhance the permeability, bioavailability, and therapeutic efficacy of enclosed plant components and are now regarded as efficient nanocarrier systems for oral and topical delivery of phytochemicals in diverse indications, including cancer and other chronic disorders.[6,7,8,9]

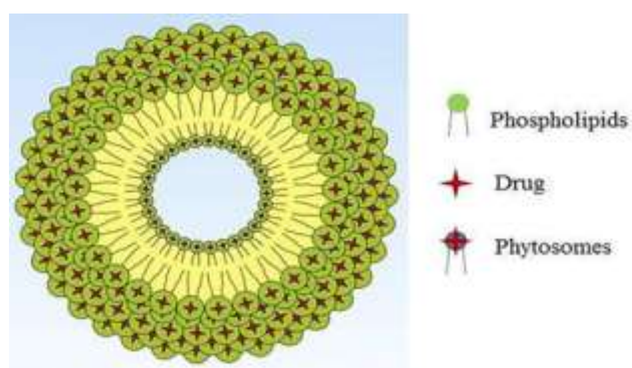

Figure 1: Structure of Phytosome[10]

3. DIFFERENCE BETWEEN PHYTOSOMES AND LIPOSOMES

Table: 1 Difference between Phytosomes and Liposomes

Feature	Phytosomes	Liposomes	Citation
Basic nature	Molecular complex of phytochemical with phospholipid	Closed phospholipid bilayer vesicle	9,11
Main purpose	Enhance solubility, permeability and bioavailability of herbal phytochemicals	General carrier for many hydrophilic and lipophilic drugs	9,11,12
Drug location	Phytochemical closely associated with/complexed to phospholipid (improves membrane affinity)	Drug dissolved in aqueous core or within bilayer, not necessarily complexed	7,13
Typical cargo	Plant polyphenols and other phytochemicals (e.g., silymarin, quercetin)	Small-molecule drugs, peptides, nucleic acids, extracts, etc.	9,11,14
Bioavailability effect	Often produces large increases in oral or topical bioavailability vs. free extract	Improves delivery but effect depends strongly on formulation and drug	9,14
Stability & release	Good interaction with phytochemicals; release can be faster than liposomes	Often higher physical stability with slower release	13
Example applications	Meriva®(Curcumin Phytosome) used for Anti-inflammatory, joint health, and antioxidant support	Doxil® (Doxorubicin HCl Liposome Injection for Treatment of ovarian cancer, AIDS-related Kaposi's sarcoma, and multiple myeloma.	15,16

4. COMPONENTS OF PHYTOSOME

I. Phytoconstituent / plant extract (hydrophilic part)

- Standardized plant extract or pure phytochemical, most often polyphenols such as flavonoids, terpenoids, tannins, xanthones
- Examples: Silymarin, Quercetin, Catechin, Curcumin, Green Tea Polyphenols, Ginsenosides [2,17,18]

II. Phospholipid (lipid component)

- Core structural component; usually phosphatidylcholine (PC) from soy or egg[3,19]
- Other phospholipids that can be used: phosphatidylethanolamine, phosphatidylserine, phosphatidylinositol[3,20].

Phytosomes are formed by hydrogen bonding between the polar head of the phospholipid and polar groups (–OH, –COOH, $–NH_2$) of the phytoconstituent[2,21,22]

III. Solvent system (for complex formation)

- Complex is produced by reacting extract and phospholipid in aprotic or non-polar organic solvents such as dioxane, acetone, ethanol, methanol, chloroform, dichloromethane, or hexane, depending on method [2,11,21,23]
- Solvent is later removed (rotary evaporation, lyophilization), leaving the solid phytosomal complex[2,21].

IV. Optional excipients (formulation dependent)

- Stabilizers / antioxidants (e.g., vitamin E, butylated hydroxytoluene) to protect lipids and polyphenols from oxidation [24,25]

- Cryoprotectants like mannitol or sugars when freeze-drying[26]
- Surfactants or polymers in advanced systems to adjust surface charge or stability [24,25]

5. METHODS OF PREPARATION OF PHYTOSOMES FOR HERBAL DRUG DELIVERY

Phytosomes are prepared by reacting herbal extracts or purified phytoconstituents with phospholipids (mainly phosphatidylcholine) in suitable organic solvents, then removing the solvent and processing the resulting phyto-phospholipid complex into a dosage form. The main methods used for herbal drug delivery are solvent evaporation / thin-film hydration, anti-solvent precipitation, solvent ether injection, co-solvent lyophilization / freeze-drying and spray-drying[6,27–30]

1. Solvent Evaporation/ Thin-Film Hydration

In the solvent evaporation / thin film method, the extract and phospholipid are dissolved in a common organic solvent (e.g., methylene chloride, dioxane, ethanol), often in a 1:1 or 1:2 molar ratio, then the solvent is removed under reduced pressure to form a thin film or solid complex that can be hydrated to give phytosomal vesicles[6,29,31] This is the most commonly reported technique for phytosomes of silymarin, ginkgo, green tea, and many other herbal drugs [2,6,32]

2. Anti Solvent Precipitation

In anti solvent precipitation, the extract–phospholipid solution in a miscible organic solvent is added to a non solvent (e.g., n hexane), leading to precipitation of the complex, which is then filtered and dried[28,30,31]

3. Solvent Ether Injection

Solvent ether (or solvent) injection involves injecting an organic solution of phospholipid and phytoconstituent into an aqueous phase, where rapid diffusion of solvent induces spontaneous formation of nano sized phytosomes [27,28]

4. Freeze Drying / Co Solvent Lyophilization

To improve stability and handling, these primary complexes can be further processed by freeze drying or co solvent lyophilization, in which the organic solvent is removed and the dispersion is lyophilized, often with cryoprotectants[27–29]

5. Spray Drying / Vacuum Drying

Spray drying or vacuum drying are also used to obtain free flowing phytosomal powders suitable for solid oral dosage forms. [29,30]Choice of method affects particle size, entrapment efficiency, yield and release behaviour, and is selected according to the herbal drug's solubility and the intended route (oral, topical, transdermal).[28,33,34]

6. KEY CHARACTERISATION / EVALUATION PARAMETERS FOR PHYTOSOMES

For herbal phytosome products, characterisation focuses on confirming complex formation, nanosystem quality, and in vitro performance.

1. Basic physicochemical characterisation

Core critical quality attributes:

- **Particle size & size distribution (PDI)**

Dynamic light scattering is routinely used to determine mean size and polydispersity; size strongly influences stability, skin/oral absorption and biodistribution[2,9,35]

- **Zeta potential (surface charge)**

Indicates electrostatic stability; sufficient magnitude (positive or negative) helps prevent aggregation and predicts shelf stability and behavior at biological interfaces [2,35,36]

- **Morphology and lamellarity**

Transmission and scanning electron microscopy (TEM/SEM) provide information on vesicle shape, surface, and uni-/multilamellar structure, important for release behavior and stability.[2,9,37]

- **Chemical composition and complex formation**

FTIR, DSC, NMR and X ray diffraction are used to confirm interactions (H bonding, ionic interactions) between phytoconstituents and phospholipids and to distinguish true phytosomes from simple physical mixtures.[9,19,37]

2. Encapsulation and drug loading

- **Encapsulation efficiency (EE%) and drug loading**

Quantified (typically by HPLC/UV) after separating free drug (dialysis, ultracentrifugation); EE% is a key indicator of formulation success and strongly affects dose and bioavailability.[9,35,36]

3. In vitro performance tests

- **In vitro release profile**

Dialysis or diffusion studies in biorelevant media are used to determine release kinetics; sustained or improved release vs. crude extract is usually targeted.[9,12,35]

- **Stability studies**

Monitoring size, PDI, zeta potential, EE%, and chemical integrity over time under different temperatures, pH, and light conditions evaluates physical/chemical stability and suitability for scale up.[2,9,36,38]

4. Biological evaluation (preclinical/clinical)

- **Permeation/uptake studies**

Cell or skin models (for topical) and Caco 2/intestinal models (for oral) assess enhanced permeability versus plain extracts.[7,9,39]

- **Pharmacokinetics and bioavailability**

Animal or human studies measuring Cmax, AUC, and t½ show consistently higher systemic exposure for phytosomes of curcumin, silymarin, quercetin and others compared with non complexed extracts.[6,9,24,29]

- **Pharmacodynamic/therapeutic endpoints**

Disease specific models (anti inflammatory, anticancer, hepatoprotective, metabolic, etc.) compare efficacy and required dose versus conventional herbal formulations.[8,9,12,24]

- **Safety/biocompatibility**

Cytotoxicity assays and in vivo toxicity profiles confirm that phospholipid complexes remain biocompatible and do not introduce new adverse effects relative to the parent herb.[24,36,38]

7. ADVANTAGES AND LIMITATIONS PHYTOSOMES FOR HERBAL PRODUCTS

Phytosomes are phospholipid–plant extract complexes designed to overcome poor bioavailability of many herbal actives.

Advantages

- Greatly enhanced bioavailability and absorption of poorly absorbed polyphenols (e.g., silymarin, curcumin, quercetin, resveratrol) versus crude extracts or simple capsules [9,35,40]

- Improved solubility and permeability across lipid-rich biological membranes (gut, skin), giving higher tissue levels at lower doses[7,8,12,35]
- Protection from degradation (acid, enzymes, oxidation), leading to better stability and shelf life than conventional herbal formulations[7,24,35]
- Dose sparing and fewer side-effects: higher pharmacological activity at reduced doses, with good biocompatibility due to use of physiological phospholipids [9,34,35,40,41]
- Versatile dosage forms: can be formulated as capsules, tablets, syrups, gels, creams and cosmetics [7,29,35]
- Food-grade/ nutraceutical positioning and existence of successful marketed products (e.g. Siliphos, Meriva, Greenselect, Casperome) support translational potential [7,9,35]

Limitations and challenges

- **Formulation and stability issues:** some systems are pH-sensitive, prone to instability or rapid drug leakage, complicating large-scale production and storage [7,9,12,42,43]
- **Scale-up and manufacturing control:** maintaining particle size, loading and reproducibility during industrial production is difficult; quality control must be rigorous[9,42]
- **Limited and heterogeneous clinical evidence:** many data are preclinical; few well-designed head-to-head clinical trials versus non-phytosomal extracts exist, so superiority is not fully established across indications[9,40]
- **Regulatory and cost barriers:** classification between drug/nutraceutical, lack of specific guidelines, and higher production costs may restrict broad adoption[24,42,43]
- **Safety still needs long-term validation:** components are generally regarded as safe, but more chronic-use and high-dose clinical studies are required[38,43]

8. MARKETED PHYTOSOMAL PRODUCTS FOR HERBAL DRUGS

A number of phytosome-based herbal products are already commercialized, mainly through the Indena "phytosome/ herbosome/ planterosome" platforms and similar technologies.

Table 2: Representative marketed phytosome products and indications.

Product / trade name	Main herb / active	Main indication / use	Citations
Siliphos (silybin phytosome) / Legalon SIL, Silipide	Silybum marianum (silymarin/silybin)	Hepatoprotection in chronic liver disease, toxic liver injury, NAFLD; improved oral bioavailability vs. plain silymarin	9,39,44
Meriva / Curcumin phytosome	Curcuma longa (curcumin)	Anti-inflammatory and antioxidant; arthritis, joint pain, metabolic and cardiovascular support	9,25,35
Greenselect / GreenSelect Phytosome	Camellia sinensis (green tea catechins)	Weight management, metabolic syndrome, antioxidant and cardiovascular support	6,9,35
Ginkgoselect / Ginkgo biloba phytosome	Ginkgo biloba extract	Cognitive function, peripheral vascular disease, microcirculation	6,9,45,46

Leucoselect / grape seed phytosome	Vitis vinifera (proanthocyanidins)	Cardiovascular protection, antioxidant, capillary fragility	9,25,29
Mirtoselect / bilberry phytosome	Vaccinium myrtillus (anthocyanins)	Vision support, capillary health	6,9
Boswellia phytosome (e.g. Casperome)	Boswellia serrata acids	Anti-inflammatory, osteoarthritis, IBD adjunct	9,12,35
Ginseng, hawthorn, rutin, catechin phytosomes	Panax ginseng, Crataegus spp., etc.	Tonic, cardioprotective, antioxidant and cosmetic uses	6,29,46

9. RECENT ADVANCES IN PHYTOSOMES FOR HERBAL DRUG DELIVERY

1) Nanostructured and modified phytosomes

- **Nano-phytosomes and nanostructured phytosomes**: downsizing to nanometer range enhances surface area, cellular uptake, and enables more precise control of release and targeting[12,25,35]
- **Surface-modified/stealth phytosomes** (e.g., PEGylated, polymer-coated) are being explored to prolong circulation, reduce RES uptake and enable tumor or inflamed-tissue targeting, especially in cancer applications[8,12,24,35]
- **Food-grade and biopolymer hybrid systems**: encapsulation of phytosomes into biopolymers (maltodextrin, gums, other GRAS excipients) via spray-drying has improved stability, flow properties and shelf life for oral and functional-food use[35,47]

2) Therapeutic expansion

- Strong growth in anticancer phytosomes (curcumin, quercetin, silybin, genistein, berberine, etc.), often as chemo-sensitizers or toxicity-reducing adjuncts[8,12,24]
- Increasing work on topical phytosomes for anti-aging, photoprotection, wound healing and dermal delivery of polyphenols, with superior skin penetration vs. conventional extracts and liposomes[6,7,9,29,46]
- Exploration in neurodegenerative, cardiometabolic, infectious and wound-healing indications, taking advantage of improved bioavailability and tissue targeting[12,38]

10. FUTURE PROSPECTS

Across recent reviews, several converging directions are highlighted:

- **Intelligent / stimuli-responsive phytosomes**: systems responsive to pH, redox or enzymes to release phytochemicals selectively at tumor or inflamed sites are proposed as a next step[24,35]
- **Personalised and precision herbal medicine**: combining phytosomes with pharmacogenomics and disease phenotyping to tailor botanical combinations and doses to individuals[2,35]
- **Combination and co-loaded phytosomes**: multi-herb or herb-drug co-encapsulation (e.g., curcumin + other polyphenols or chemotherapeutics) to exploit synergy and reduce conventional drug dosage[8,24,35]
- **Regulatory-grade manufacturing and quality control**: emphasis on scalable,

reproducible processes (e.g., spray drying, continuous manufacturing), robust characterization and ICH-compatible stability to transition from nutraceuticals to prescription phytopharmaceuticals[9,25,48]

- **Expanded clinical translation**: reviews repeatedly call for larger, well-designed RCTs directly comparing phytosomes with non-phytosomal herbal products to confirm advantages in hard clinical endpoints rather than just PK improvements [8,24,38]

Overall, phytosomes are positioned as a maturing platform that already supports multiple marketed herbal products, with current research pushing toward nano-engineered, targeted and personalized phytosomal systems capable of meeting pharmaceutical regulatory standards.

CONCLUSION

Phytosome technology represents an important advancement in herbal drug delivery by overcoming key limitations of conventional formulations, such as poor solubility, permeability, and bioavailability of phytoconstituents. Complexation with phospholipids enhances the absorption, stability, and therapeutic efficacy of bioactive compounds like curcumin, silymarin, quercetin, and green tea polyphenols while maintaining safety due to the biocompatible nature of phospholipids. Phytosomes have demonstrated improved pharmacokinetic and pharmacodynamic profiles across various therapeutic applications, including hepatoprotection, inflammation, cancer, cardiovascular disorders, and cosmeceuticals, with several products already commercialized. Despite these advantages, challenges related to large-scale manufacturing, quality control, regulatory approval, and limited clinical evidence remain, highlighting the need for standardized production methods and well-designed clinical trials. Overall, phytosomes effectively bridge traditional herbal medicine and modern nanotechnology, offering a promising platform for future phytopharmaceutical and nutraceutical development

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