Frontiers in Health Informatics
ISSN-Online: 2676-7104
www.healthinformaticsjournal.com
2024; Vol 13
Open Access

Phytosomes: A Novel Drug Delivery System For Enhanced Bioavailability Of Herbal Drugs

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Cite this paper as: Swati Saxena, Janki Prasad Rai (2024) Phytosomes: A Novel Drug Delivery System For Enhanced Bioavailability Of Herbal Drugs. *Frontiers in Health Informatics*, 386-400

Abstract
Herbal medicines possess immense therapeutic potential due to their diverse bioactive phytoconstituents; however, their clinical utility is often limited by poor aqueous solubility, low membrane permeability, rapid metabolism, and reduced bioavailability. Conventional dosage forms fail to effectively deliver many plant-derived compounds such as flavonoids, polyphenols, terpenoids, and alkaloids across biological membranes. To overcome these limitations, novel drug delivery systems (NDDS) have emerged, among which phytosomes have gained significant attention as an advanced and efficient approach for herbal drug delivery. Phytosomes are phospholipid-based molecular complexes formed by the interaction of phytoconstituents with phospholipids, particularly phosphatidylcholine, resulting in enhanced lipophilicity, stability, and absorption. Unlike liposomes, phytosomes involve chemical complexation rather than physical entrapment, leading to superior bioavailability and therapeutic performance. This review comprehensively discusses the concept, mechanism, composition, methods of preparation, and characterization of phytosomes. It also highlights their advantages, applications in pharmaceutical, nutraceutical, and cosmeceutical fields, recent technological advancements, and associated limitations. Additionally, recent literature on phytosomal and herbal formulations is summarized to emphasize their growing clinical and commercial relevance. Overall, phytosome technology represents a promising strategy to maximize the therapeutic potential of phytopharmaceuticals and bridge the gap between traditional herbal medicine and modern drug delivery systems.
Keywords: Phytosomes, Herbal drug delivery, Phytophospholipid complex, Bioavailability enhancement, Novel drug delivery system, Phytochemicals, Nanotechnology in herbal medicine.

Introduction
Herbal medicines have been widely used for centuries due to their therapeutic potential and minimal side effects. However, the clinical application of many herbal drugs is limited by poor absorption, rapid metabolism, and low bioavailability of phytoconstituents such as flavonoids, polyphenols, terpenoids, and alkaloids. Conventional dosage forms fail to deliver these compounds effectively across biological membranes (Verma and Singh; 2008).
To address these challenges, novel drug delivery systems (NDDS) such as liposomes, niosomes,

transferosomes, ethosomes, and phytosomes have been developed. Among these, phytosomes represent a promising and innovative approach for enhancing the delivery of herbal drugs. The term "phytosome" is derived from the Greek words *phyto* (plant) and *soma* (cell-like structure). In phytosomes, the phytoconstituent forms a stable complex with phospholipids through hydrogen bonding, resulting in improved membrane permeability and bioavailability (Mahomoodally et al., 2021).

Concept of Phytosomes

Phytosomes are a novel drug delivery system designed to enhance the bioavailability and therapeutic efficacy of plant-derived active constituents, especially polyphenols, flavonoids, terpenoids, and other phytochemicals that exhibit poor absorption when administered orally (Chaudhary and Rajora; 2025). The term *phytosome* is derived from "phyto" (plant) and "some" (cell-like structure), indicating a vesicular system in which the phytoconstituent is complexed with phospholipids. Unlike conventional herbal extracts or liposomes, phytosomes form a molecular complex between the phytochemical and phospholipid, resulting in improved stability, better membrane permeability, and enhanced systemic availability (Baishya et al., 2019).

Most phytochemicals are hydrophilic in nature and possess large molecular sizes, which limit their ability to cross lipid-rich biological membranes. Phytosome technology addresses this limitation by converting these polar molecules into lipid-compatible forms without altering their pharmacological activity (Jacob et al., 2025). Phosphatidylcholine is commonly used as the carrier due to its biocompatibility, amphiphilic nature, and additional hepatoprotective properties. The resulting phytosome complex exhibits superior absorption compared to free phytoconstituents, making it a promising approach for herbal drug delivery.

Mechanism of Phytosomes

The mechanism of phytosomes is based on the formation of a stable molecular complex between the phytochemical and phospholipid through hydrogen bonding and polar interactions. In this system, the polar functional groups of the phytoconstituent (such as hydroxyl, carboxyl, or keto groups) interact with the polar head of the phospholipid, while the non-polar fatty acid chains of the phospholipid orient outward. This unique arrangement imparts lipid solubility to the phytoconstituent, facilitating its passage across lipid-rich cell membranes (Barani et al., 2021).

Upon oral administration, phytosomes readily integrate with the phospholipid bilayer of intestinal epithelial cells due to their structural similarity to biological membranes. This enhances intestinal absorption via passive diffusion, leading to improved bioavailability. Additionally, the phospholipid component protects the phytoconstituent from degradation in the gastrointestinal tract, thereby improving stability and systemic circulation time. Once absorbed, the phytosome complex dissociates, releasing the active phytochemical at the target site to exert its pharmacological effect.

The phytosome mechanism ensures enhanced permeability, improved stability, and better therapeutic outcomes compared to conventional herbal formulations. This makes phytosomes an effective and

innovative delivery system for maximizing the clinical potential of phytopharmaceuticals (Tripathy et al., 2013).

Composition of Phytosomes

Phytosomes are composed primarily of a bioactive phytoconstituent and a phospholipid, which together form a stable molecular complex. The phytoconstituent usually consists of plant-derived active compounds such as flavonoids, polyphenols, terpenoids, alkaloids, glycosides, or tannins. These compounds are responsible for the therapeutic activity of the herbal formulation but often suffer from poor bioavailability due to their hydrophilic nature and large molecular size. In phytosome systems, the phytoconstituent acts as the core active ingredient and is complexed with the phospholipid to improve its lipid compatibility and membrane permeability.

The most commonly used phospholipid in phytosome formulation is phosphatidylcholine, derived from natural sources such as soybean or sunflower lecithin. Phosphatidylcholine is preferred because of its excellent biocompatibility, amphiphilic nature, and ability to form strong hydrogen bonds with phytoconstituents. Additionally, phosphatidylcholine itself exhibits biological benefits, including hepatoprotective and membrane-stabilizing properties, which further enhance the therapeutic value of the phytosome formulation. The phospholipid component forms the structural backbone of the phytosome complex and plays a critical role in enhancing absorption (Gaikwad et al., 2023).

Organic solvents are another important component involved in the preparation of phytosomes. Solvents such as ethanol, methanol, acetone, dichloromethane, or tetrahydrofuran are commonly used to dissolve both the phytoconstituent and phospholipid during complex formation. These solvents facilitate intimate molecular interaction between the components and are later removed during the formulation process. The choice of solvent depends on the solubility characteristics of the phytochemical and the phospholipid, as well as safety and regulatory considerations (Golzardi and Glamočlija; 2025).

In some formulations, additional excipients may be incorporated to improve stability, handling, or delivery performance. These may include antioxidants (such as α-tocopherol) to prevent phospholipid oxidation, stabilizers to enhance shelf life, or carriers like polymers for incorporation into dosage forms such as capsules, tablets, gels, or creams. However, unlike liposomal systems, phytosomes generally do not require surfactants or cholesterol, as the stability is primarily achieved through phytoconstituent–phospholipid complexation (Barani et al., 2021).

Methods of Preparation of Phytosomes

Phytosomes are generally prepared by forming a molecular complex between a standardized plant extract or isolated phytoconstituent and a phospholipid, usually phosphatidylcholine. The preparation methods are simple, reproducible, and mainly rely on solvent evaporation or complexation techniques. The commonly employed methods are described below.

Solvent Evaporation Method

The solvent evaporation method is the most widely used technique for phytosome preparation. In this method, the phytoconstituent and phospholipid are dissolved separately or together in an appropriate organic solvent such as ethanol, methanol, acetone, or dichloromethane. The resulting solution is then

subjected to evaporation under reduced pressure using a rotary evaporator. As the solvent is removed, a thin film of phytoconstituent–phospholipid complex is formed. The dried mass is further pulverized and stored in airtight containers. This method promotes strong hydrogen bonding between the polar functional groups of the phytoconstituent and the phospholipid, resulting in a stable phytosomal complex (Maryana et al., 2016).

Anti-Solvent Precipitation Method

In the anti-solvent precipitation method, the phytoconstituent and phospholipid are dissolved in a common organic solvent to form a clear solution. This solution is then slowly added to a non-solvent (anti-solvent) such as n-hexane or petroleum ether under continuous stirring. The phytosome complex precipitates out due to reduced solubility in the anti-solvent. The precipitate is collected by filtration and dried under vacuum. This method is simple, economical, and suitable for scale-up (Ahmad et al., 2017).

Reflux Method

In the reflux method, the phytoconstituent and phospholipid are dissolved in a suitable solvent and heated under reflux for a specific period, usually 1–2 hours. Continuous heating enhances molecular interaction between the components and ensures complete complex formation. After refluxing, the solvent is removed by evaporation, and the resulting phytosome complex is dried and collected. This method is particularly useful for phytoconstituents requiring thermal energy to achieve effective complexation (Singh et al., 2018).

Thin-Film Hydration Technique

The thin-film hydration method involves dissolving the phytoconstituent and phospholipid in an organic solvent mixture, followed by evaporation under reduced pressure to form a thin film on the walls of a round-bottom flask. The dried film is then hydrated using distilled water or buffer with gentle agitation. Hydration results in the formation of phytosomal vesicles. This method is useful when phytosomes are intended for vesicular drug delivery systems or topical formulations (Maryana et al., 2016).

Co-Solvent Lyophilization Method

In this method, both the phytoconstituent and phospholipid are dissolved in a co-solvent system, typically ethanol and water. The solution is frozen and then lyophilized to remove the solvent, yielding a dry phytosome powder. Lyophilization helps preserve the structural integrity of the phytosome complex and improves long-term stability (Freag et al., 2013).

Characterization of Phytosomes

Characterization of phytosomes is essential to confirm the formation of the phytoconstituent–phospholipid complex and to evaluate its physicochemical properties, stability, and performance. Various analytical and instrumental techniques are employed for this purpose.

Particle Size and Polydispersity Index (PDI)

Particle size and size distribution of phytosomes are determined using dynamic light scattering (DLS). The particle size influences bioavailability, stability, and cellular uptake. A low polydispersity index (PDI < 0.3) indicates uniform size distribution and good formulation homogeneity (Visht et al., 2023).

Zeta Potential

Zeta potential measurement provides information about the surface charge and stability of phytosomes. It is evaluated using a zeta potential analyzer. Higher absolute zeta potential values (positive or negative) indicate better electrostatic repulsion between particles, resulting in enhanced colloidal stability (Hooresfand et al., 2015).

Entrapment Efficiency

Entrapment efficiency represents the percentage of phytoconstituent successfully complexed within the phytosome. It is determined by separating free drug from the phytosomal formulation using centrifugation or dialysis, followed by quantitative analysis using UV-Visible spectroscopy or HPLC. Higher entrapment efficiency indicates effective complex formation (Udapurkar et al., 2018)

Fourier Transform Infrared Spectroscopy (FTIR)

FTIR analysis is performed to confirm chemical interactions between the phytoconstituent and phospholipid. Shifts or disappearance of characteristic peaks indicate hydrogen bonding and complex formation without chemical degradation of the active compound (El-Batal et al., 2018).

Differential Scanning Calorimetry (DSC)

DSC is used to study thermal behavior and crystallinity changes. The disappearance or shift of melting endotherms of the phytoconstituent in phytosomes confirms successful complexation and conversion into an amorphous or less crystalline form (El-Batal et al., 2018).

X-Ray Diffraction (XRD)

XRD analysis provides information on the crystalline or amorphous nature of phytosomes. Reduced peak intensity or disappearance of characteristic crystalline peaks of the phytoconstituent indicates successful incorporation into the phospholipid matrix (Sharma et al., 2016).

Morphological Studies

Surface morphology and shape of phytosomes are examined using scanning electron microscopy (SEM) or transmission electron microscopy (TEM). These techniques reveal vesicular structure, size, and surface characteristics of phytosomes (Hou et al., 2013).

Solubility and Partition Coefficient Studies

Solubility studies are conducted to compare the aqueous and lipid solubility of phytosomes with the plain extract. Enhanced solubility and improved partition coefficient indicate improved lipophilicity and bioavailability (Sasongko et al., 2019).

In-Vitro Drug Release Studies

In-vitro release studies are carried out using dialysis membrane techniques to assess the release pattern of the phytoconstituent from phytosomes. Phytosomal formulations generally exhibit sustained and controlled drug release compared to plain extracts (Singh et al., 2018).

Stability Studies

Stability studies are performed under different temperature and humidity conditions to assess physical and chemical stability over time. Parameters such as particle size, zeta potential, and drug content are monitored during the study period.

Advantages of Phytosomes

Phytosomes offer several significant advantages over conventional herbal extracts and other vesicular drug delivery systems. One of the major benefits of phytosomes is their ability to enhance the bioavailability of phytoconstituents. Many plant-derived compounds are poorly absorbed due to low lipid solubility and large molecular size; phytosomes form a complex with phospholipids, improving their absorption across biological membranes.

Another important advantage of phytosomes is improved stability of phytoconstituents. Complexation with phospholipids protects sensitive herbal molecules from degradation caused by light, heat, pH, and enzymatic action, thereby extending shelf life and maintaining therapeutic efficacy.

Phytosomes also provide better pharmacokinetic and therapeutic performance. Due to enhanced absorption and prolonged circulation time, phytosomes often require lower doses to achieve the desired pharmacological effect, which helps in reducing dose-related side effects.

Enhanced lipophilicity is a key advantage of phytosomes. The phytoconstituent–phospholipid complex exhibits increased affinity toward lipid membranes, facilitating improved permeation through the gastrointestinal tract, skin, or mucosal barriers, making phytosomes suitable for oral, topical, and transdermal delivery.

Phytosomes exhibit high entrapment efficiency compared to conventional vesicular systems such as liposomes. The active phytoconstituent is chemically bonded to the phospholipid rather than being physically entrapped, leading to better drug loading and reduced leakage.

Another advantage is controlled and sustained drug release. Phytosomal formulations can provide gradual release of active constituents, improving therapeutic consistency and patient compliance.

Phytosomes are generally biocompatible and safe, as they utilize natural phospholipids such as phosphatidylcholine, which is a normal component of biological membranes and also possesses hepatoprotective properties.

Additionally, phytosomes enhance the commercial and clinical value of herbal products. Improved efficacy, standardization, and reproducibility make phytosome-based formulations more acceptable in modern pharmaceutical and nutraceutical markets (Patel et al., 2009).

Applications of Phytosomes

Phytosomes have wide-ranging applications in pharmaceutical, nutraceutical, and cosmeceutical fields due to their ability to enhance the bioavailability and therapeutic efficacy of herbal constituents. They are particularly useful for delivering phytochemicals that exhibit poor solubility and limited membrane permeability.

In **oral drug delivery**, phytosomes are extensively applied to improve the absorption of herbal compounds such as flavonoids, polyphenols, alkaloids, and terpenoids. Phytosomal formulations of

curcumin, quercetin, silymarin, and resveratrol have demonstrated significantly enhanced bioavailability and improved pharmacological outcomes compared to conventional extracts.

Phytosomes are widely used in **hepatic and metabolic disorder management.** Phosphatidylcholine-based phytosomes not only enhance drug delivery but also exhibit hepatoprotective activity, making them ideal for treating liver disorders, hyperlipidemia, diabetes, and metabolic syndrome.

In **anti-inflammatory and antioxidant therapy**, phytosomes improve systemic and localized delivery of plant-based antioxidants, leading to effective scavenging of free radicals and reduction of oxidative stress. This application is particularly beneficial in chronic inflammatory diseases such as arthritis, cardiovascular disorders, and neurodegenerative conditions.

Phytosomes play a crucial role in **topical and transdermal drug delivery**. Their enhanced lipid affinity allows deeper skin penetration, making them suitable for dermatological applications including wound healing, psoriasis, acne, eczema, and skin aging. Phytosomal gels and creams have shown improved skin retention and therapeutic response.

In the field of **neurological and CNS disorders**, phytosomes facilitate better delivery of neuroprotective phytoconstituents across biological barriers. Phytosomal formulations have been explored for treating anxiety, depression, cognitive impairment, neuropathic pain, and Alzheimer's disease.

Phytosomes are increasingly used in **anticancer and chemopreventive therapy**, where improved bioavailability of phytochemicals enhances their cytotoxic and antiproliferative effects. Compounds such as curcumin, green tea polyphenols, and flavonoids exhibit improved anticancer potential when formulated as phytosomes.

In **nutraceuticals and functional foods**, phytosomes enhance the absorption of plant-based nutrients and antioxidants, leading to improved health benefits and consumer acceptance. They are commonly incorporated into dietary supplements for immune boosting, cardiovascular health, and anti-aging benefits (Gaurav et al., 2021).

Recent Advances in Phytosome Technology

In the past few years, phytosome technology has undergone rapid innovation, significantly expanding its potential as an advanced drug delivery platform for herbal and nutraceutical compounds. One major advancement is the **integration of design of experiments (DoE) and quality by design (QbD) approaches** into phytosome formulation development. By optimizing critical process and formulation variables (e.g., lipid ratio, solvent system, temperature), researchers have achieved superior entrapment efficiency, uniform particle size, and improved stability compared to traditional trial-and-error methods.

Another notable trend is the **use of novel phospholipids and lipid derivatives** beyond conventional phosphatidylcholine. Modified phospholipids, including PEGylated phospholipids and ionizable lipids, have been explored to further enhance membrane interaction, circulation stability, and targetability of phytosomes for systemic delivery.

In parallel, the **application of nanotechnology tools such as nanoprecipitation, supercritical fluid technology, and microfluidics** has enabled the production of phytosomes with highly controlled size

distributions and narrow polydispersity. These advanced manufacturing platforms improve scalability and batch-to-batch reproducibility, addressing key challenges for commercial translation.

Hybrid systems that combine phytosomes with other delivery technologies represent another frontier. For example, **phytosome-loaded invasomes, transfersomes, and nanoemulsions** have been developed to synergize the membrane-penetrating ability of phytosomes with mechanical flexibility or enhanced skin permeability, resulting in improved topical efficacy. Similarly, phytosomes integrated into **hydrogel, nanoparticle, and scaffold systems** have shown promise for localized therapeutic delivery in wound healing, arthritis, and tissue regeneration.

Recent research has also focused on **targeted and stimuli-responsive phytosomes**. By incorporating materials responsive to pH, enzymes, or redox conditions, phytosome systems have been engineered to release payloads more selectively at disease sites, such as tumors or inflammatory tissues, minimizing off-target effects and improving therapeutic indices.

Pharmacokinetic and pharmacodynamic profiling of phytosome formulations is now more routinely included in preclinical studies, with several phytosome products demonstrating improved oral absorption, enhanced plasma levels, and longer half-lives in animal models. In some cases, clinical investigations have begun to validate efficacy and safety in human populations, particularly for hepatoprotective and antioxidant phytosomes.

Limitations of Phytosomes

Despite their significant advantages in enhancing the bioavailability of phytoconstituents, phytosomes possess certain limitations that restrict their universal application. One of the primary challenges is **formulation complexity**, as the preparation of stable phytosome complexes requires precise optimization of phospholipid ratio, solvent system, temperature, and reaction time. Minor deviations during formulation can affect complex formation and reproducibility.

Another limitation is the **limited compatibility with all phytoconstituents**. Phytosome formation mainly depends on the interaction between polar functional groups of phytochemicals and phospholipids; therefore, non-polar or weakly polar compounds may not efficiently form stable phytosomal complexes, limiting the scope of drugs that can be delivered using this system.

Stability issues also pose a concern, particularly for phytosomes containing thermolabile or oxidation-sensitive phytochemicals. Phospholipids are susceptible to hydrolysis and oxidative degradation, which may compromise product stability during long-term storage unless appropriate antioxidants and protective packaging are used.

From a manufacturing perspective, **scale-up and cost** remain significant challenges. High-purity phospholipids, organic solvents, and specialized processing techniques increase production costs (Chaudhary and Rajora; 2025).

Conclusion

Phytosomes represent a promising and innovative drug delivery system designed to overcome the inherent limitations of conventional herbal formulations, particularly poor solubility, low permeability, and limited bioavailability of phytoconstituents. By forming molecular complexes between bioactive

plant compounds and phospholipids, phytosomes significantly enhance absorption, stability, and therapeutic efficacy of herbal drugs.

Extensive research has demonstrated that phytosomal formulations improve pharmacokinetic profiles, increase tissue targeting, and reduce dose-related toxicity compared to traditional extracts. Their versatility allows incorporation into various dosage forms such as capsules, tablets, gels, creams, and transdermal systems, broadening their pharmaceutical and nutraceutical applications. Additionally, the biocompatible and biodegradable nature of phospholipids contributes to their safety and patient acceptability.

Despite challenges related to formulation complexity, stability, cost, and regulatory approval, continuous advancements in nanotechnology, analytical techniques, and formulation strategies are addressing these limitations. Increasing preclinical and emerging clinical evidence further supports the potential of phytosomes as effective carriers for phytochemicals in the management of chronic and lifestyle-related disorders.

Table 1: Review of Literature on Phytosomal and Herbal Formulations

Author (Year)	Plant / Bioactive Compound	Formulation / Approach	Key Findings	Significance
Yadav et al. (2024)	*Cassia fistula* (Amaltas)	Polyherbal phytosomal gel	Improved pharmacokinetic and pharmacodynamic performance; good entrapment efficiency and sustained drug release	Demonstrated superiority of phytosomal gel over crude extract
Jabrail et al. (2024)	Rutin	Phytosomal gel	Particle size 60–180 nm; promoted 85–90% periodontal tissue regeneration	Long-lasting therapeutic effect and enhanced local immunity
Pranita et al. (2024)	Cumin seed phytoconstituents	Phytosomes → gel/tablet/cream	Improved absorption and bioavailability	Effective herbal drug delivery strategy
Agarwal & Tomar (2024)	Curcumin	DOE-optimized phytosomes	~90.83% drug release in 12 h; good compatibility	Demonstrated optimization via Design of

				Experiments
Chilka et al. (2024)	*Musa paradisiaca* peel	Phytosomal gel	Enhanced antioxidant activity; improved physicochemical properties	Validated phytosomal gel for topical use
Krishnaswami et al. (2024)	Various phytoconstituents	Phytosomes (review)	Enhanced bioavailability via phospholipid complexes	Highlighted clinical and commercial phytosomes
Toma et al. (2024)	Multiple phytoconstituents	Phytosomes (review)	Improved therapeutic efficacy and bioavailability	Supported phytosomes as adjunct therapy
Kumar et al. (2024)	Rubiadin	Oral phytosomes	134% relative bioavailability; neuroprotective effect	Addressed bioavailability limitation of anthraquinones
Mohapatra et al. (2024)	Ellagic acid, Eugenol	Phytosomes	Improved skin penetration and stability	Potential for dermatological and cosmetic use
Ware et al. (2024)	Polyherbal extracts	Polyherbal phytosomes	Enhanced synergistic therapeutic effect	Promising for novel herbal DDS
Ramachandran et al. (2023)	*Crotalaria biflora*	Phytosomal gel	Good pH, viscosity, spreadability	Effective topical anti-inflammatory formulation
Shrivastava et al. (2023)	Various phytoconstituents	Phytosomes	Improved pharmacokinetics	Versatile herbal DDS
Burjwal et al. (2023)	*Morinda citrifolia*	Phytosomes	Improved entrapment and stability	Enhanced therapeutic efficiency
Solanki et al. (2023)	*Tabernaemontana divaricata*	Phytosomes	Increased antioxidant activity	Preservation of bioactivity
Peeriga et al. (2023)	Polyphenols	Phytosomes (review)	Improved bioavailability at low doses	Potential for cancer therapy

Amit et al. (2023)	Naringin	Phytosomes	Sustained drug release (87.96%)	Improved delivery of flavonoids
Saonere et al. (2023)	*Glycyrrhiza glabra*	Phytophospholipid complex	Enhanced antioxidant and antimicrobial activity	Improved therapeutic potential
Deleanu et al. (2023)	Ginger & Rosehip	Phytosomes	Improved bioavailability and anti-inflammatory activity	Effective oral phytosomal delivery
Singh et al. (2022)	*Alstonia scholaris*	Phytosomes	Enhanced antidiabetic potential	Improved herbal therapy outcomes
Chen et al. (2022)	Herbal extracts	Phytosomes / Transferosomes	Superior skin penetration	Advanced vesicular DDS

Conclusion

Phytosomes have emerged as a highly promising and innovative drug delivery system to overcome the major limitations associated with conventional herbal formulations, particularly poor solubility, low permeability, and reduced bioavailability of phytoconstituents. By forming stable molecular complexes between plant-derived bioactive compounds and phospholipids, phytosomes significantly enhance membrane permeability, stability, and therapeutic efficacy without altering the intrinsic pharmacological activity of the phytochemicals.

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