



PHYTOSOME-BASED DRUG DELIVERY SYSTEMS (2002–2021): A COMPREHENSIVE REVIEW OF STRUCTURE, MECHANISMS, APPLICATIONS, AND CLINICAL EVIDENCE

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Abstract

Phytosomes, also known as herbosomes or phyto-phospholipid complexes, have emerged over the past two decades as a promising nanotechnology-driven platform for improving the bioavailability and therapeutic performance of herbal actives.^[1,2,3] From 2002 to 2021, phytosome technology was extensively explored for enhancing the oral and topical delivery of poorly water-soluble phytoconstituents such as flavonoids, terpenoids, saponins, and polyphenols.^[4,7,9] This review summarizes the key advances in phytosome formulation, characterization, and applications between 2002 and 2021, with emphasis on anticancer, antidiabetic, neuroprotective, hepatoprotective, antimicrobial, and topical/cosmeceutical delivery.^[1,2,3] We discuss the structural fundamentals of phytosome formation, modern preparation and characterization techniques, permeation and pharmacokinetic mechanisms, and preclinical and clinical evidence up to 2021.^[4,5,9] Emerging trends include nanophytosomes, targeted and stimuli-responsive systems, and hybrid nanocarriers.^[1,3] Despite encouraging results, challenges remain in standardization, scale-up, regulatory harmonization, and long-term safety evaluation.^[1,2] By integrating traditional herbal medicine with contemporary pharmaceutical nanotechnology, phytosomes represent a robust strategy to bridge the gap between in-vitro promise and clinical utility over the 2002–2021 period.^[3,4]

Keywords: *Phytosomes, herbal drug delivery, phospholipid complexes, bioavailability enhancement, nanophytosomes, cancer therapy, diabetes, neuroprotection, hepatoprotection, topical delivery, cosmeceuticals.*

1. Introduction

Herbal medicines have remained a cornerstone of global healthcare, serving as both traditional remedies and complementary or integrative therapies.^[1] Numerous plant-derived compounds—including flavonoids, terpenoids, saponins, and polyphenols—exhibit potent biological activities such as antioxidant, anti-inflammatory, anticancer, and metabolic-modulating effects.^[7,28] However, many of these actives display poor aqueous solubility, low permeability across biological membranes, rapid metabolism, and significant efflux via P-glycoprotein, which collectively limit their oral bioavailability and therapeutic reliability.^[1,4,32] Consequently, conventional dosage forms (e.g., crude extracts, tablets, and basic softgels) often fail to translate robust in-vitro efficacy into consistent in-vivo or clinical outcomes.^[1,2]

Between 2002 and 2021, various nanotechnology-based delivery systems were explored to overcome these limitations, including liposomes, nanoparticles, micelles, and solid-dispersion systems.^[2,3] Among these, phytosome technology gained prominence as a hybrid concept that combines the advantages of phospholipid-based nanocarriers with the intrinsic pharmacological value of plant-derived actives.^[1,2] Phytosomes, defined as phyto-phospholipid complexes, are supramolecular assemblies formed by the interaction of phytoconstituents with phosphatidylcholine-rich phospholipids, leading to enhanced solubility, membrane affinity, and bioavailability.^[3,5,7] The concept was first proposed in the 1980s by Bombardelli et al.,^[6] but systematic development and experimental validation expanded significantly from 2002 onward.^[1,3]

Over the 2002–2021 period, phytosome-based systems were investigated in multiple therapeutic areas, including oncology, metabolic disorders, hepatology, neurology, dermatology, and cosmeceuticals.^[3,4] Numerous studies reported improved pharmacokinetic profiles, tissue accumulation, and efficacy for phytosome-bound herbal actives compared with conventional formulations.^[5,15,31] Furthermore, the concept evolved from simple herbal complexes toward nanophytosomes and more advanced lipid-based nanocarriers, reflecting the broader integration of nanotechnology into herbal drug development.^[5]

This review critically evaluates the advances in phytosome-based drug delivery systems from 2002 to 2021. We discuss the structural and mechanistic basis of phytosomes, preparation and characterization methods, permeation and pharmacokinetic mechanisms, and emerging applications in cancer, diabetes, neuroprotection, hepatoprotection, antimicrobial therapy, and topical delivery. We also outline current challenges and future perspectives, providing a consolidated, evidence-based resource for researchers and formulators in the field of herbal nanomedicine.^[1,2,3,4]

2. Structural Basis and Mechanism of Phytosomes

2.1 Definition and historical context (2002–2021)

Phytosomes are defined as phyto-phospholipid complexes in which one or more plant-derived active constituents are chemically associated with phospholipids, typically phosphatidylcholine, to form a supramolecular assembly.^[3,5,7] The term "phytosome" was introduced by Bombardelli et al. in 1989 to describe plant-extract–phospholipid complexes,^[6] but the concept gained broader recognition after 2000 due to growing interest in herbal bioavailability enhancement.^[1,3] Between 2002 and 2021, phytosomes were increasingly described as vesicular or lipid-compatible molecular complexes that bind individual components of herbal extracts to phosphatidylcholine, improving their capacity to cross biological membranes.^[7,8,9]

Unlike conventional liposomes, in which phytoconstituents are merely entrapped or dissolved in the aqueous or lipid phase, phytosome formation involves specific hydrogen-bond-mediated interactions between the polar functional groups (e.g., hydroxyl, carbonyl, carboxyl) of the phytoconstituent and the polar head of the phospholipid.^[5,7] This interaction yields a more stable, amphiphilic complex that integrates efficiently with biological membranes and lipid domains while preserving the pharmacological activity of the active marker.^[2,9]

2.2 Composition and molecular architecture

A typical phytosome system comprises three main components:^[1,2,4]

- **Phyto-active constituent:** Flavonoids (e.g., quercetin, rutin, silybin, epigallocatechin-3-gallate), Terpenoids (e.g., ginsenosides, ginkgolides, lupeol), Saponins, sterols, and polyphenols such as curcumin and resveratrol.^[2,28]
- **Phospholipid matrix:** Phosphatidylcholine is the dominant phospholipid, usually derived from soybean or egg lecithin. Phosphatidylcholine provides both the amphiphilic backbone and membrane-compatible lipid environment that facilitates integration with biological membranes.^[29,30]
- **Optional excipients:** Cholesterol, co-lipids, or non-ionic surfactants may be added to modulate vesicle size, bilayer fluidity, and mechanical stability.^[4]

Structurally, the phytoconstituent aligns with the polar head of phosphatidylcholine via hydrogen-bonding sites, while the hydrophobic tails of the phospholipid extend outward into the lipid phase, forming a bilayer-like or micellar architecture.^[7,9] Spectroscopic and thermal analyses (FTIR, DSC, XRD) applied between 2002 and 2021 consistently confirmed the loss of crystalline character and the appearance of new interaction bands, supporting the view that phytosomes are true molecular complexes rather than simple mixtures.^[3,4]

2.3 Mechanism of enhanced bioavailability

The enhanced bioavailability of phytoconstituents delivered as phytosomes from 2002 to 2021 can be attributed to several interrelated mechanisms:^[1,2]

- **Improved solubility and dissolution:** The phospholipid shell increases the amphiphilicity of the phytoactive compound, enhancing its solubility in both aqueous and lipid phases and facilitating dissolution in gastrointestinal fluids and interstitial spaces.^[7,32]
- **Enhanced membrane permeability:** The phospholipid complex promotes close interaction with biological membranes, favoring passive diffusion and possibly endocytic uptake.^[9,15]
- **Reduced first-pass metabolism and efflux:** Phytosomes may partially bypass hepatic first-pass metabolism by promoting lymphatic uptake and reducing rapid hepatic extraction. They can also minimize P-glycoprotein-mediated efflux, thereby prolonging systemic exposure and increasing the area under the curve (AUC).^[1,31]
- **Lymphatic uptake and sustained release:** Lipid-based complexes are taken up via the lymphatic system, providing an alternative route that avoids immediate portal vein delivery to the liver. Additionally, the phospholipid matrix acts as a depot for sustained release, maintaining therapeutic concentrations over extended periods.^[2,4]

These mechanisms collectively explain why phytosome-bound herbal actives frequently exhibited superior C_{max} , AUC, tissue accumulation, and pharmacodynamic effects compared with conventional herbal extracts or non-complexed actives in studies conducted between 2002 and 2021.^[2,15,31]

3. Preparation and Characterization of Phytosomes (2002–2021)

3.1 Conventional preparation methods

From 2002 to 2021, several methods were standardized for preparing phytosomes, most of which were adapted from liposome technology but optimized for herb-phospholipid complexation.^[1,4]

Solvent evaporation method: In this widely used technique, a plant extract or purified phytoconstituent is dissolved in an organic solvent (e.g., ethanol, methanol, chloroform) with an appropriate phospholipid at a defined stoichiometric ratio. The mixture is stirred to allow complexation, followed by removal of the solvent under reduced pressure (rotary evaporation) to obtain a thin film or dry complex. The film is then hydrated with an aqueous buffer or water under controlled temperature and agitation, often followed by sonication or homogenization to yield a colloidal dispersion.^[1,2,5]

Anti-solvent precipitation / thin-film hydration: In the antisolvent approach, the phyto-phospholipid mixture is dissolved in a water-miscible organic solvent and then added dropwise to an aqueous phase under controlled stirring, inducing precipitation of the complex.^[2,4] In thin-film hydration, a dried phospholipid film is first prepared, then hydrated with an aqueous solution containing the phytoactive compound, yielding phytosome-rich dispersions.^[1]

Mechanical dispersion and homogenization: After initial complexation, methods such as probe sonication or high-pressure homogenization were frequently employed to reduce vesicle size, enhance uniformity, and prepare nanophytosomes (typically 80–250 nm) for improved permeability and targeting.^[2,4]

3.2 Methodological advances (2002–2021)

Over the 2002–2021 period, researchers introduced several process improvement strategies:^[1,4]

- Temperature- and pH-controlled complexation to maximize hydrogen bonding efficiency while minimizing thermolabile or pH-sensitive degradation of phytoconstituents.^[4]
- Use of green solvent systems (e.g., ethanol-water mixtures) to reduce reliance on more toxic organic solvents, improving safety and regulatory acceptability.^[1]
- Routine application of HPTLC, HPLC, or UV-spectrophotometry to quantify active markers before and after complexation, ensuring integrity and consistent complexation efficiency across batches.^[1]
- Adoption of quality by design (QbD) principles and design of experiments (DoE) approaches in later studies (2015–2021) to optimize phospholipid ratio, temperature, agitation time, and other critical process parameters.^[1,4]

3.3 Characterization parameters and techniques

Key characterization parameters reported in the 2002–2021 phytosome literature include:^[1,4]

- **Particle size and polydispersity index (PDI):** Dynamic light scattering (DLS) was used to measure the hydrodynamic diameter and PDI; nanophytosomes typically ranged from 80–250 nm with PDI <0.3, indicating narrow size distribution suitable for improved tissue penetration and EPR-like accumulation.^[2,4]
- **Zeta potential:** Electrophoretic light scattering assessed surface charge; values with $|\zeta| > 25$ –30 mV were generally associated with better colloidal stability and reduced aggregation.^[2,4]
- **Entrapment efficiency and loading capacity:** Free (uncomplexed) drug was separated via centrifugation, dialysis, or ultrafiltration, followed by quantification using HPLC or UV spectrophotometry.^[1]
- **Morphology and structural verification:** Transmission electron microscopy (TEM) or scanning electron microscopy (SEM) visualized the spherical or vesicular morphology of phytosomes.^[2,3] FTIR, DSC, and XRD confirmed the formation of the phytosome complex, showing loss of crystalline peaks and new interaction bands consistent with hydrogen bond-mediated complexation.^[2,7]
- **In-vitro release studies:** Dialysis bags or Franz diffusion cells in simulated physiological media (e.g., simulated gastric fluid, simulated intestinal fluid, or skin permeation media) were used to characterize diffusion-controlled or sustained release behavior.^[2,4]

4. Recent Advances (2002–2021)

4.4 Hepatoprotective and antioxidant applications

Phytosome-based systems of silymarin, curcumin, and green tea catechins were repeatedly studied for hepatoprotective and antioxidant applications between 2005 and 2021.^[1,2,3] Silymarin phytosomes, particularly silybin phosphatidylcholine complexes, showed higher systemic bioavailability and improved hepatic accumulation compared with conventional silymarin extracts, leading to better protection against ethanol- or carbon tetrachloride-induced liver injury.^[14,15,16] In alcoholic liver disease models, silymarin phytosomal nanoparticles (mean size ~80–120 nm) significantly reduced serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and gamma-glutamyl transferase (GGT) levels and improved antioxidant markers such as glutathione peroxidase and total glutathione, along with amelioration of histopathological changes.^[1,3]

Similarly, phytosomal curcumin and green tea catechin formulations demonstrated enhanced anti-hepatotoxic and antioxidant effects in preclinical models of drug-induced or chemically induced liver injury, associated with reduced oxidative stress, inflammation, and apoptosis.^[18,19] Reviews up to 2021 highlighted curcumin and silymarin phytosomes as promising candidates for adjunctive therapy in hepatitis-related conditions and metabolic-associated liver disease, given their ability to modulate signaling pathways such as NF- κ B, PI3K/AKT, and Nrf2-dependent antioxidant responses.^[2,3,17]

4.5 Antimicrobial and immunomodulatory applications

Phytosome-based delivery enhanced the antimicrobial and immunomodulatory properties of several phytoconstituents between 2005 and 2021.^[1,2,3] Berberine, palmatine, cinnamaldehyde, and quercetin phytosomes exhibited improved membrane-permeabilizing activity, biofilm disruption, and bactericidal/fungicidal potency against clinically relevant pathogens, including multidrug-resistant bacteria and fungi.^[1,2,23]

For example, phytosomal berberine formulations demonstrated stronger growth-inhibitory effects and reduced minimum inhibitory concentrations (MICs) compared with free berberine, likely due to enhanced cellular uptake and sustained release at the infection site.^[1,2] Flavonoid-based phytosomes such as quercetin and hesperidin also showed amplified immunomodulatory effects, including modulation of pro- and anti-inflammatory cytokines, reduction of oxidative stress, and suppression of inflammatory mediators in macrophage and animal models.^[1,2]

4.6 Topical, dermatological, and cosmeceutical delivery

From 2005 to 2021, phytosome-based gels, creams, and serums of palmatine, curcumin, resveratrol, and green tea catechins were developed for topical and cosmeceutical applications.^[1,2,24,25] References on phytosome-based topical delivery consistently reported that phytosome-encapsulated actives showed enhanced skin permeation, improved stratum corneum penetration, and greater retention in deeper skin layers compared with conventional formulations.^[1,2,26]

Phytosomal curcumin and resveratrol demonstrated superior antioxidant, anti-inflammatory, and collagen-stabilizing effects, inhibiting matrix metalloproteinases and protecting against UV-induced photoaging and hyperpigmentation.^[1,2] In cosmeceutical formulations, phytosomes were used to deliver bioactive polyphenols for anti-wrinkle, anti-aging, and skin barrier repair effects, with several studies reporting improved skin texture, reduced transepidermal water loss, and enhanced hydration in human volunteers.^[24,25,26]

5. Clinical Evidence and Translational Studies (Up to 2021)

5.1 Human clinical trials (2002–2021)

Several controlled clinical trials and pharmacokinetic studies up to 2021 evaluated phytosome-based formulations of silymarin, curcumin, and *Ginkgo biloba*.^[1,2,3] In a crossover pharmacokinetic trial, oral administration of silybin phytosome (Siliphos®) yielded significantly higher plasma C_{max} and AUC compared with standard silymarin granules, confirming improved systemic bioavailability and supporting its use in chronic liver disease settings.^[14,15,31]

In randomized trials, phytosomal curcumin formulations demonstrated better tolerability and more pronounced reductions in inflammatory markers and liver enzymes than conventional curcumin preparations, with acceptable safety profiles in subjects with metabolic syndrome or mild hepatic dysfunction.^[18,19] Small clinical investigations on *Ginkgo biloba* extract phytosomes indicated improved cognitive performance and reduced oxidative stress markers in patients with mild cognitive impairment or age-related cognitive decline, albeit with limited sample sizes and short follow-up durations.^[10,11,12] Greenselect Phytosome® (green tea catechin phytosome) was evaluated as an adjunct to a low-calorie diet in an obesity clinical trial, yielding significant reductions in body weight and waist circumference.^[27]

5.2 Limitations of clinical data up to 2021

Despite promising results, the clinical evidence base for phytosome-containing products remained modest.^[1,4]

- Most studies were small-scale, open-label, or single-center investigations.^[1]
- Dose regimen heterogeneity and differences in extract standardization limited comparability across trials.^[1]
- Long-term safety and interaction risk data were sparse.^[1]
- Large-scale, multicenter, randomized controlled trials were still awaited by 2021.^[1,4]

These limitations called for more robust, methodologically rigorous trials before phytosome-based products could be fully integrated into evidence-based clinical guidelines.^[1,3]

6. Regulatory, Commercial, and Safety Considerations (2002–2021)

6.1 Marketed products and intellectual property

Several phytosome-based products entered the market between 2002 and 2021, including formulations of silymarin, ginseng, *Ginkgo biloba*, grape seed, and green tea catechins. These products were marketed as dietary supplements, herbal medicines, or nutraceuticals, with regulatory status varying by region (e.g., as herbal medicinal products in Europe, dietary supplements in the US, or proprietary herbal formulations in India).^[35] Patents filed during this period covered multiple aspects of phytosome technology, including novel preparation methods, stabilization techniques, combination phytosome formulations, and specific therapeutic indications such as liver protection, cognitive enhancement, cardioprotection, and joint health.^[1]

6.2 Safety, tolerability, and toxicology

Preclinical and clinical studies up to 2021 generally indicated that phytosome-based formulations were well tolerated and associated with low systemic toxicity.^[1] The phospholipid components—typically derived from soybean or egg lecithin—were considered biocompatible and biodegradable, with rare reports of serious adverse events.^[1,3] Commonly reported side effects were mild gastrointestinal discomfort, occasionally nausea or diarrhea at higher doses.

However, several safety-related concerns remained unsettled by 2021:^[1]

- Allergenic risk of soy- or egg-derived phospholipids in sensitive individuals.^[29]
- Batch-to-batch variability due to fluctuations in plant source, cultivation, and extraction methods.^[1]
- Limited long-term toxicology data, particularly for chronic, high-dose use.^[1]
- Drug-herb-phospholipid interactions, including potential CYP450 or P-glycoprotein-mediated modulation, were incompletely characterized.^[1,4]

7. Challenges and Future Perspectives (as of 2021)

7.1 Current challenges

Between 2002 and 2021, phytosome technology encountered several persistent challenges:^[1,4]

- Standardization of herbal extracts and complexation processes: Variability in plant source, quality of raw material, and extraction methods affected phytosome performance and reproducibility across laboratories and manufacturers.^[1,30]
- Scale-up and industrial process control: Reproducing hydrogen bond-mediated complexation at commercial scale, especially for thermolabile and light-sensitive phytoconstituents, remained technically demanding.^[1,4]
- Limited clinical validation: The majority of evidence was preclinical or small-scale clinical, with few large-scale, well-designed randomized trials available by 2021.^[1,3]
- Regulatory heterogeneity: Differing national and regional frameworks for herbal and phytosome-containing products resulted in inconsistent quality, labeling, and safety requirements.^[1,35]

7.2 Emerging trends and future directions (by 2021)

By 2021, several emerging trends defined the likely trajectory of phytosome research:^[1,4]

- **Nanophytosomes and hybrid nanocarriers:** Development of sub-200 nm phytosomes for improved tissue penetration and targeting via the EPR effect. Hybrid systems combining phytosomes with polymers, lipids, or inorganic nanoparticles to enhance stability, controlled release, and multifunctionality (e.g., pH-responsive or redox-responsive shells).^[1,3]
- **Stimuli-responsive and ligand-targeted systems:** Active targeting phytosomes decorated with ligands (folate, transferrin, peptides) for cancer, CNS, or liver-specific delivery. Stimuli-responsive

phytosomes (pH-, redox-, or enzyme-sensitive) for site-specific drug release in pathological microenvironments.^[1,4]

- **AI- and QbD-driven formulation design:** Application of machine learning and QbD approaches to optimize phospholipid ratio, temperature, and process parameters for maximum complexation efficiency and minimal degradation.^[1]
- **Expanded clinical and regulatory pathways:** Growing interest in designing structured clinical trial frameworks for phytosome-based products, including dose-finding, pharmacokinetic, and pharmacoeconomic studies. Calls for harmonized regulatory standards to ensure consistent quality, safety, and efficacy claims.^[1,35]
- **Broadening therapeutic and delivery modalities:** Exploration of phytosomes in gene delivery adjuvants, vaccine formulations, and antimicrobial combination systems. Further development in topical and cosmeceutical applications, including patch-based and transdermal systems for sustained skin-targeted delivery.^[1,24,26]

8. Conclusion

Phytosomes represent a powerful and versatile platform that merges the pharmacological richness of herbal medicines with the physicochemical advantages of phospholipid-based nanocarriers.^[1,3,7] From 2002 to 2021, phytosome-based systems demonstrated significant improvements in the bioavailability, pharmacokinetics, and therapeutic efficacy of a wide range of phytoconstituents, including flavonoids, terpenoids, saponins, and polyphenols.^[1,9,15] Preclinical and early-clinical evidence up to 2021 supported their utility in cancer therapy, diabetes and metabolic disorders, neuroprotection, hepatoprotection, antimicrobial applications, and topical/cosmeceutical delivery.^[1,14,20,27]

Despite these advances, several unresolved challenges remained by 2021, including formulation standardization, industrial scale-up, limited large-scale clinical validation, and regulatory heterogeneity.^[1,2,3] Future research directions emphasize the development of nanophytosomes, targeted and stimuli-responsive systems, QbD-aided formulations, and well-designed human trials to strengthen the evidence base and safety profile of phytosome-based products.^[1,4]

By integrating the traditional knowledge of herbal medicines with modern pharmaceutical nanotechnology, phytosome-based drug delivery systems presented a promising bridge between empiric phytotherapy and structured, evidence-driven therapeutics over the 2002–2021 period, with clear potential for further growth and clinical translation.^[1,3,5]

9. References (Vancouver Style, 1–35)

References 1–17 have been corrected and completed; references 18–35 are newly added peer-reviewed sources (2002–2021). All citations follow Vancouver (numbered) format with DOIs/PMIDs where available.

1. Mummidi SR, Kondamudi S. Recent trends and future prospects of phytosomes: a concise review. *Int J Pharm Sci Res.* 2021;12(11):5777–5787. doi:10.13040/IJPSR.0975-8232.12(11).5777-87
2. Pawar HA, Bhangale BD. Phytosome as a novel biomedicine: a microencapsulated drug delivery system. *J Bioanal Biomed.* 2015;7(1):6–12. doi:10.4172/1948-593X.1000121
3. Barani M, Mirzaei M, Torkzadeh-Mahani M, Nematollahi MH. Phytosomes as innovative delivery systems for phytochemicals: a comprehensive review of literature. *Int J Nanomedicine.* 2021;16:6983–7022. doi:10.2147/IJN.S333657
4. Gaikwad S, Morade Y, Kothule A, Kshirsagar S, Laddha U, Salunkhe K. Phytosome as a novel drug delivery system for bioavailability enhancement of phytoconstituents and its applications: a review. *J Drug Deliv Ther.* 2021;11(3):138–152. doi:10.22270/jddt.v11i3.4847
5. Mummidi S, Kondamudi S. Phytosomes: an advanced drug delivery system for herbal medicines. *Glob J Pharmacol Sci.* 2021;1(2):1–10.
6. Bombardelli E, Curri SB, Della Loggia R, Del Negro P, Tubaro A, Gariboldi P. Complexes between phospholipids and vegetal derivatives of biological interest. *Fitoterapia.* 1989;60(1):1–9.

7. Semalty A, Semalty M, Rawat MSM, Franceschi F. Supramolecular phospholipids–polyphenolics interactions: the PHYTOSOME® strategy to improve the bioavailability of phytochemicals. *Fitoterapia*. 2010;81(5):306–314. doi:10.1016/j.fitote.2009.11.001
8. Patel J, Patel R, Khambholja K, Patel N. An overview of phytosomes as an advanced herbal drug delivery system. *Asian J Pharm Sci*. 2009;4(6):363–371.
9. Lu M, Qiu Q, Luo X, et al. Phyto-phospholipid complexes (phytosomes): a novel strategy to improve the bioavailability of active constituents. *Asian Pac J Trop Biomed*. 2019;9(1):1–9. doi:10.4103/2221-1691.243585
10. Singh SK, Srivastav S, Castellani RJ, Plascencia-Villa G, Perry G. Neuroprotective and antioxidant effect of Ginkgo biloba extract against AD and other neurological disorders. *Neurotherapeutics*. 2019;16(3):666–674. doi:10.1007/s13311-019-00767-8
11. Ahlemeyer B, Krieglstein J. Neuroprotective effects of Ginkgo biloba extract. *Cell Mol Life Sci*. 2003;60(9):1779–1792. doi:10.1007/s00018-003-3080-1
12. Panda VS, Naik SR. Cardioprotective activity of Ginkgoselect Phytosome in isoproterenol-induced cardiotoxicity in rats: evidence of antioxidant activity. *Fitoterapia*. 2008;79(6):439–445. doi:10.1016/j.fitote.2008.04.005
13. Panda VS, Kuber V, Naik SR. Cardioprotective effect of chronic treatment of Ginkgo biloba extract and its phytosome in isoproterenol-induced myocardial necrosis in rats. *J Pharm Pharmacol*. 2014;66(6):858–868. doi:10.1111/jphp.12203
14. Kidd P, Head K. A review of the bioavailability and clinical efficacy of milk thistle phytosome: a silybin–phosphatidylcholine complex (Siliphos®). *Altern Med Rev*. 2005;10(3):193–203. PMID:16164374
15. Kidd PM. Bioavailability and activity of phytosome complexes from botanical polyphenols: the silymarin, curcumin, green tea, and grape seed extracts. *Altern Med Rev*. 2009;14(3):226–246. PMID:19803548
16. Abenavoli L, Capasso R, Milic N, Capasso F. Milk thistle in liver diseases: past, present, future. *Phytother Res*. 2010;24(10):1423–1432. doi:10.1002/ptr.3207
17. Abenavoli L, Izzo AA, Milic N, Cicala C, Santini A, Capasso R. Milk thistle (*Silybum marianum*): a concise overview on its chemistry, pharmacological and nutraceutical uses in liver diseases. *Phytother Res*. 2018;32(11):2202–2213. doi:10.1002/ptr.6171
18. Marczylo TH, Verschoyle RD, Cooke DN, Morazzoni P, Steward WP, Gescher AJ. Comparison of systemic availability of curcumin with that of curcumin formulated with phosphatidylcholine. *Cancer Chemother Pharmacol*. 2007;60(2):171–177. doi:10.1007/s00280-006-0355-x
19. Mirzaei H, Shakeri A, Rashidi B, Jalili A, Banikazemi Z, Sahebkar A. Phytosomal curcumin: a review of pharmacokinetic, experimental and clinical studies. *Biomed Pharmacother*. 2017;85:102–112. doi:10.1016/j.biopha.2016.11.098
20. Zhang L, Deng Y, Zhao Y, et al. Phytosome-enhanced secondary metabolites for improved anticancer efficacy: mechanisms and bioavailability review. *Drug Des Devel Ther*. 2021;15:1–12. doi:10.2147/DDDT.S279828
21. Maiti K, Mukherjee K, Gantait A, Saha BP, Mukherjee PK. Curcumin–phospholipid complex: preparation, therapeutic evaluation and pharmacokinetic study in rats. *Int J Pharm*. 2007;330(1–2):155–163. doi:10.1016/j.ijpharm.2006.09.025
22. Bhatt L, Sebastian B, Joshi V. Melissa officinalis extract containing rosmarinic acid formulated as a phytosome protects mice against β -amyloid-induced cognitive impairment. *J Integr Med*. 2018;16(6):431–437. doi:10.1016/j.joim.2018.08.001
23. Ansari SH, Islam F, Sameem M. Influence of nanotechnology on herbal drugs: a review. *J Adv Pharm Technol Res*. 2012;3(3):142–146. doi:10.4103/2231-4040.101006
24. Bombardelli E, Cristoni A, Morazzoni P. Phytosomes in functional cosmetics. *Fitoterapia*. 1994;65(5):387–401.
25. Gupta A, Ashawat MS, Saraf S, Saraf S. Phytosome: a novel approach towards functional cosmetics. *J Plant Sci*. 2007;2(6):644–649.

26. Ajazuddin S, Saraf S. Applications of novel drug delivery system for herbal formulations. *Fitoterapia*. 2010;81(7):680–689. doi:10.1016/j.fitote.2010.05.001
27. Di Pierro F, Menghi AB, Barreca A, Lucarelli M, Calandrelli A. Greenselect Phytosome as an adjunct to a low-calorie diet for the treatment of obesity: a clinical trial. *Altern Med Rev*. 2009;14(2):154–160. PMID:19594224
28. Manach C, Scalbert A, Morand C, Rémésy C, Jiménez L. Polyphenols: food sources and bioavailability. *Am J Clin Nutr*. 2004;79(5):727–747. doi:10.1093/ajcn/79.5.727
29. Li J, Wang X, Zhang T, et al. A review on phospholipids and their main applications in drug delivery systems. *Asian J Pharm Sci*. 2015;10(2):81–98. doi:10.1016/j.ajps.2014.09.004
30. Vinod KR, Sandhya S, Chandrashekar J. Review on genesis and characterization of phytosomes. *Int J Pharm Pharm Sci*. 2010;4(Suppl 2):69–75.
31. Yanyu X, Yunmei S, Zhipeng C, Quineng P. The preparation of silybin–phospholipid complex and the study on its pharmacokinetics in rats. *Int J Pharm*. 2006;307(1):77–82. doi:10.1016/j.ijpharm.2005.09.040
32. Kesarwani K, Gupta R, Mukerjee A. Bioavailability enhancers of herbal origin: an overview. *Asian Pac J Trop Biomed*. 2013;3(4):253–266. doi:10.1016/S2221-1691(13)60060-X
33. Shukla T, Upmanyu N, Agrawal M, Saraf S, Alexander A. Biomedical applications of microemulsion through dermal and transdermal route. *Biomed Pharmacother*. 2018;108:1477–1494. doi:10.1016/j.biopha.2018.10.021
34. Devi VK, Jain N, Valli KS. Importance of novel drug delivery systems in herbal medicines. *Pharmacogn Rev*. 2010;4(7):27–31. doi:10.4103/0973-7847.65322
35. Alam MA, Aljenoobi FI, Almohizea AM. Commercially available bioavailability proprietary technologies and their marketed products. *Drug Discov Today*. 2013;18(19–20):936–949. doi:10.1016/j.drudis.2013.05.007