Pharmacognosy Reviews, 2024; 18(36):117-126.
www.phcogrev.com

Review Article

A Comparative Investigation on the Phytosomes of Diverse Bioactive Nootropic Medicinal Herbs

Ram Chhatrapati Vighne*, Sharada Laxman Deore, Bhushan Arun Baviskar

Government College of Pharmacy, Amravati, Maharashtra, INDIA.

ABSTRACT

The word "phyto" means plants and the word "somes" means cellular structures. Phytosomes are a type of a vesicular delivery system based on lipids that solves the problem of the low bioavailability of hydrophilic phytoconstituents. Phytosomes being lipid-rich bio membranes exhibits higher bioavailability than simple plant extracts. Phytosomes found very effective in hepatoprotection. The main way that phospholipids and the active phytochemical work together is through the establishment of hydrogen bonds among the polar components of the phytoconstituent and the polar parts of the phospholipids. The phytosome structure can be thought of as a cell, which protects the bioactive parts of the plant extract from being broken down by digestive juices and intestinal bacteria before reaching to target site. Plants and derived preparations have been used to keep human healthy since ancient times. There are many benefits of herbal drugs. These benefits include making the drug more soluble and bioavailable, protecting it from toxicity, increasing its pharmacological activity, making it more stable, spreading it out more in tissue macrophages, giving it for a longer time and protecting it from physical or chemical derivatization. Because phytosomes are more lipid-soluble, they are easier to absorb through the skin and the digestive system. This means that they can pass through cellular membranes, which makes them more bioavailable at the site of action. This review elaborates the phytosome components, methods of preparations, benefits and examples.

Keywords: Phytosome, Phospholipid, Bioavailability and Soya-Lecithin.

Correspondence:
Mr. Ram Chhatrapati Vighne
Department of Pharmacognosy,
Government College of Pharmacy,
Amravati, Maharashtra, INDIA.
Email: rampharmacy14@gmail.com

Received: 30-07-2024;
Revised: 13-08-2024;
Accepted: 30-10-2024.

INTRODUCTION

The utilization of phytosome technology as a medicine carrier was first proposed in 1989. Phytoconstituents that are soluble in water have the ability to undergo a conversion process, resulting in the formation of a molecular complex that is compatible with lipids. This complex is commonly referred to as phytosomes.[1,2] Phytosomes have higher bioavailability compared to basic herbal extracts as a result of their improved ability to traverse lipid-rich bio membranes and enter the circulatory system. The use of phytosome technology has demonstrated significant advancements in the therapeutic utilization of botanical polyphenols, as it has been observed that greater bioavailability typically leads to improved effectiveness.[1] The therapeutic efficacy of phospholipids utilized in the phytosome formulation as a hepatoprotection has been observed. The primary interaction that takes place between the phospholipids and the active substance involves the establishment of hydrogen bonds between the polar regions of the phytoconstituent and the polar phospholipids. The presence of this link confers enhanced stability to the phytosome formula in comparison to liposomes.[3] Furthermore, it should be noted that drug delivery systems operating at the nanoscale level offer distinct advantages when compared to conventional methods. The decrease in particle size has been observed to enhance the rate of dissolution and solubility, which is frequently associated with an enhancement in the drug's *in vivo* performance. The user's text is already academic and does not need to be rewritten.[4,5] Phytosomes refer to sophisticated herbal liposomes that are created through the conjugation of specific constituents of herbal extracts with phosphatidylcholine.[6] The phytosome is a proprietary method developed by Indena, which involves the incorporation of phospholipids into standardized concentrates, resulting in a significant improvement in their absorption and utilization.

The phytosome structure, which may be thought of as a self-contained living entity, protects the medicinal components of the herbal extract from breakdown by digestive secretions and intestinal microbes. Phytochemical compounds that possess water solubility exhibit the capacity to undergo a conversion into a complex with lipids, hence earning the label of phytosomes. The procedure entails the application of different readily available plant extracts, particularly phytochemicals, that enable the direct

DOI: 10.5530/phrev.20241898

Publishing Partner : Manuscript Technomedia. [www.mstechnomedia.com]

bonding of these substances to phosphatidylcholine. This suggests that the binding of choline molecules to phytochemicals is followed by the encapsulation of the choline-bound material within the fat-soluble phosphatidyl moiety, which consists of a head and a tail. The outcome is the formation of a diminutive microsphere or cell.[7] The application of phospholipids or excipients to augment the bioavailability and therapeutic effectiveness of plant constituents with limited absorption has emerged as a viable and highly efficient approach in the realm of plant medicine formulation. The current process entails the combination of phospholipid particles containing phosphatidylcholine with standardized herbal extracts and particular bioactive plant constituents. The primary objective of this relationship is to augment multiple characteristics of phospholipid particles, encompassing membrane structure, permeability, water-oil partition coefficient, bioavailability, solubility, ability to traverse cell membranes, protection against toxicity and stability enhancement.[8,9] The development of innovative herbal dosage forms, such as phytosomes, is imperative in order to achieve cytotoxic efficacy while minimizing adverse effects, hence potentially enhancing the survival rates of individuals afflicted with breast cancer.[10]

Phytomedicine preparations have been used for health maintenance since antiquity. Phytomedicines have numerous therapeutic applications. Most biologically active phytoconstituents are found to be highly polar or water-soluble compounds; examples include flavonoids and terpenoids. Due to their poor lipid solubility, these highly water-soluble constituents are inadequately absorbed, thereby preventing them from crossing the highly lipid-rich biological membrane, resulting in poor bioavailability. Numerous techniques for enhancing bioavailability have been devised, involves the utilization of solubility and bioavailability enhancers, structural alterations and encapsulation using lipophilic carriers.[11,12] The morphology of all phytosome vesicles is seen to be spherical in nature. The production of this structure occurs when the choline head of the phosphatidylcholine molecule binds to the phytoconstituent, causing the fat-soluble segment of phosphatidylcholine to enclose the choline-bound material. Consequently, the outcome is the creation of miniature cells, like missiles, inside an aqueous environment.[13] Using innovative drug delivery systems can increase bioavailability.[14,15] The novel pharmacokinetic and pharmacodynamic profile of the alternative herbal extract surpasses that of the conventional extract, leading to enhanced bioavailability.[16,17] The health-care sector is currently placing significant emphasis on the health preventative potential of nutraceuticals. This shift in paradigm within the business involves a transition from a primary focus on treatment to a greater emphasis on prevention. The design of oral delivery systems has become vital for ensuring long-term compliance with the usage of nutraceuticals. The user provided a numerical reference without any accompanying text. The development of phytosomes is extensively utilized and documented in order to enhance medicinal effectiveness.[18-20] The mentioned characteristics provide phytosomes a promising option for the oral administration of phytochemicals that possess restricted solubility in aqueous environments and limited ability to be absorbed into the systemic circulation.[21]

Merits of Phytosomes Over Conventional Drug Delivery System

1. It facilitates the uptake of lipid-insoluble polar phytoconstituents through both oral and topical routes of delivery, resulting in improved bioavailability and consequently greater therapeutic efficacy.[19-21]
2. The bioavailability is increased due to the presence of a phospholipid complex.
3. High lipophilicity is associated with increased penetrability, making it a preferred characteristic in beauty care products compared to liposomes.
4. Phytosomes have been employed for the delivery of hepatoprotective flavonoids due to their ability to enhance bioavailability through this technology.
5. The phytosomal system has passive characteristics, lacks invasiveness and possesses potential for prompt commercialization. The dosage requirement is decreased as a result of enhanced absorption of the primary component.
6. Chemical bonds are established between the atom of phosphatidylcholine and the phytoconstituent of the plant, resulting in improved stability characteristics of the phytosomes.
7. The dosage requirement is decreased.
8. One of the advantages is the increased entrapment efficiency.
9. Phytosomes have been shown to effectively deliver drugs to target tissues.
10. Phytosomes have a higher level of efficacy when compared to liposomes in the context of skin care products.
11. The limited solubility of phytosomes in aqueous solutions facilitates the creation of enduring emulsions and creams.
12. Enhances the solubility of bile towards the herbal ingredient.
13. Phytosomes possess the nutritional advantage of containing phospholipids.
14. The ability to readily traverse the cell membrane and gain entry into the cell is observed.

Phytosomal formulation additives

Lipids: Dipalmitoyl phosphatidylcholine, distearyl phosphatidylcholine, phosphatidylcholine from soy, phosphatidylcholine from eggs and so on.[22,23]

Vesicle-forming ingredient: Aprotic Use a solvent like dioxane, acetone, or methylene chloride. Put to work as a solvent.

Non-solvent: the aliphatic hydrocarbons (like n-hexane) and the non-solvents. It is a complex precipitating solvent.

Alcohol: Ethanol, Methanol.

Buffering agent: The solution used in this study is a saline phosphate buffer with a pH of 6.5. A 7% (v/v) ethanol tris buffer solution with a pH of 6.5 was prepared. It is employed as a substance for hydration purposes.

Formulation methods of phytosomes

The phytosome is a cellular structure that is formed through the combination of soy phosphatidylcholine with standardized extracts containing polyphenolic compounds, thereby augmenting their absorption and utilization.

General method of phytosomes preparation

Phospholipids Dissolved in organic solvent containing drug.

↓

Thin film form.

↓

Hydration.

↓

Phytosome suspension formation.

↓

Steps that are usually taken to make phytosomes.[18,21]

Structure of Phytosome

Phytochemicals and some derivatives known as phytosomes. The term "phyto" refers to the bioactive component of a complex that is generated from plants, although some sources suggest that its structure bears resemblance to cells shown in Figure 1. Phytosome complexes are facilitated by lipophilic media. The chemical structures of these substances have a resemblance to cellular membranes and facilitate the transportation of phytolipids.[21]

Following are the methods which are used for the preparation of phytosomes

A. Solvent evaporation technique.

B. Super Critical Fluid (SCF) method.

C. Gas anti-solvent technique.

D. Solution-Enhanced Dispersion (SEDS).

E. Anti-solvent precipitation technique.

F. Rotary Evaporation Technique

Solvent evaporation method

Solvent evaporation in alcoholic or organic solvents prepares the combination of plant extracts or active components with dietary phospholipids. The medicinal drug and phospholipids are placed in a flask with tetrahydrofuran or ethanol in this experiment. After that, the reaction is allowed to continue at a suitable temperature for a defined time to maximize yield and drug entrapment. The formulation was chilled and analyzed.[23]

Supercritical Fluid (SCF) technique

Supercritical Fluids (SCF) are an efficient way to produce 5-2000 nm particles. Various supercritical fluid approaches have been used to improve low-solubility medication candidates. The compressed antisolvent method is one.[23,24]

Supercritical Antisolvent method (SAS)

The utilization of solution growth in Supercritical fluids (RESS), Gas Anti-Solvent technology (GAS) and the solution growth method have been observed as prominent approaches in many academic studies. Supercritical Fluid Enhanced Dispersion (SEDS) is a phenomenon characterized by the improved dispersion achieved by the utilization of supercritical fluids. The synthesis of complexes extensively relied on two Self-Consistent Field (SCF) methodologies, namely the Gaussian Atomic orbital (GAS) approach and the Self-consistent Electron Density (SEDS) method. The gas anti-solvent method involves the dissolution of the medication and phospholipids in a supercritical antisolvent,

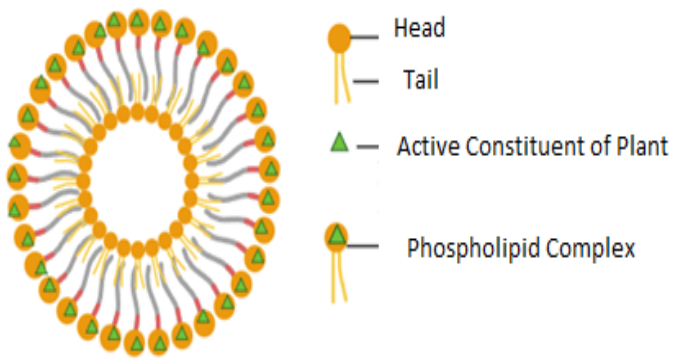

Figure 1: Phytosome Structure.

with the final pressure being controlled by the addition of additional antisolvent. Subsequently, the reaction vessel is maintained at a temperature of 38°C and a pressure of 10 mPa for duration of 3 hr, during which no mechanical stirring is employed.[25,26]

Solution Enhanced Dispersion by Supercritical fluids (SEDS)

The liquid solution and the supercritical antisolvent are introduced in a continuous manner into the precipitation unit using this particular approach. The carbon dioxide gas is introduced into the mixture of phospholipids and puerarin in the solvent using a nozzle with a diameter of 0.1 mm. The experimental parameters were optimized in order to attain ideal conditions, encompassing a temperature of 35°C, a pressure of 10 mPa, a drug to phospholipids mass ratio of 1% and a puerarin concentration of 100 mg/mL.[27]

Anti-solvent precipitation method

The anti-solvent precipitation method has been extensively applied by researchers, employing n-hexane as the antisolvent to induce precipitation of the drug-phospholipid complex from the organic solvent.[27]

Rotary evaporation technique

A fixed amount of medicine and soya lecithin was dissolved in 30 mL of tetrahydrofuran using a rotary round bottom flask. The resulting mixture was subjected to stirring for duration of 3 hr at a controlled temperature below 40°C. After collecting a thin film of the sample, n-hexane was poured on top and stirred with a magnetic stirrer. The resultant precipitate was collected, placed in an amber-colored glass bottle and left at room temperature for storage.[28,29]

Salting out method

Aprotic solvents like dioxane or acetone are used to dissolve the phytoconstituent or standardized extract in phosphatidylcholine. The resulting solution is agitated overnight and the complex is then separated by precipitation using a non-solvent, such as n-hexane.[29,30]

Lyophilization technique

Natural and synthetic phospholipids, as well as phytoconstituents, require different solvents for dissolution. After that, the solution containing the phytoconstituents is combined with the phospholipid solution. The mixture is stirred until complex formation occurs. The resultant complex is extracted using the process of lyophilization. Phytosomes are manufactured using phospholipids with acyl groups that can be either identical or distinct within phosphatidylcholine, phosphatidylserine and phosphatidylethanolamine. These phospholipids are mostly obtained from palmitic, stearic, oleic and linoleic acids. The active principle is safely connected to the polar head of the phospholipid, making the integration of the phytosome formulation into the membrane structure much easier.[31]

Mechanical Dispersion method

The experimental approach involves the introduction of lipids, which have been dissolved in an organic solvent, into an aqueous phase containing the drug. The initial stage entails the dissolution of Phytoconstituents (PC) in diethyl ether. This solution is then introduced into an aqueous solution at a regulated pace to achieve encapsulation. The creation of a compound of phyto-phospholipids follows the elimination of the organic solvent via lowered pressure. The synthesis of phospholipid complexes involves the application of innovative methods, including the use of Supercritical Fluids (SCF). Examples of methods include Gas Anti-Solvent (GAS) technology, Compressed Anti-solvent (PCA) processing and Supercritical Anti-Solvent (SAS) technology.[32,33]

Pharmaceutical Scope of phytosomes

Delivered orally or topically, phytosomes have been shown to increase the absorption of polar phytoconstituents that are insoluble in lipids. This improves bioavailability and, as a result, therapeutic effectiveness. The utilization of phytosomes technology results in an enhancement in drug entrapment efficiency. The reduction in dose requirement can be attributed to the enhancement in active constituent absorption. Soy phosphatidylcholine, utilized in the formulation of phytosomes, exhibits hepatoprotective properties, hence contributing to the synergistic effects observed when combined with other hepatoprotective compounds. The utilization of phytosomes has been found to enhance the transdermal absorption of phytoconstituents and some phytosome derived from medicinal plant mention in Table 1.[19,34,35]

Phytosomes derived from a wide variety of medicinal herbs

Mechanism of phytosomes formation

Numerous studies have shown that the polyphenolic compounds found in plant extracts can bind directly to phosphatidylcholine. Phytosomes are formed when phospholipids, like soy phosphatidylcholine, react with the standard extract or polyphenolic components, including simple flavonoids, in an aprotic solvent. The phosphatidyl moiety of phosphatidylcholine has a lipophilic nature, whereas the choline moiety has a hydrophilic nature. Phosphatidylcholine is a molecule that has both properties. The choline moiety of the phosphatidylcholine complex establishes associations with these molecules, while the lipid-soluble phosphatidyl component, which comprises the primary body and tail, encloses the choline-associated material in a more specific manner. Consequently, the presence of phyto molecules leads to the formation of a molecular entity known as a phyto-phospholipid complex, which is distinguished by its

lipid solubility and its interaction with phospholipids. Certain spectroscopic methods can be utilized to create a connection between phyto molecules and the polar choline head of phospholipids through the development of chemical interactions. Nevertheless, the results mentioned chemical analysis suggest that the phytosome complex commonly comprises a flavonoid molecule that is bound to at least one phosphatidylcholine

Table 1: Phytosome of herbs and its active constituents.

Sl. No.	Name of herb/Plant	Active constituent	Dose	Activity	References
1.	*Aloe vera*	Alloin	-	Anti-cancer activity.	[1]
2.	*Bacopa monneeri*	Bacopaside	-	Anti-amnesic activity.	[4]
3.	*Silybum morianum*	Silymarin	-	Hepatoprotective activity.	[5]
4.	*Ginkgo biloba*	Isoproterenol	85 mg/kg	Cardioprotective and antioxidant activity.	[6]
5.	*Annona muricata* Linn	Monoamine oxidase A	-	Antioxidant and anti-inflammatory stress biomarkers, neuroactive agent.	[7]
5.	Gingerol (with soya lecithine with chitosan)	Gingerol	-	For the treatment of respiratory infection.	[8]
6.	*Cedrus deodaru* bark	Taxifoline	-	Breast cancer and antioxidant.	[10]
7.	Pomegranate peels	Polyphenolic phytoconstituents	-	Protection of digestive secretion and gut microbe.	[11]
8.	*Arjuna* bark	Quercetin	-	Antiproliferative activity.	[12]
9.	Bitter melon	Charantin	-	Hypoglycaemic effect.	[13]
10	Umbelliferone	Umbelliferone	-	Photoprotective and antioxidant activity.	[14]
11.	*Syzygium cumini*	Jambosine, gallic acid	-	Antidiabetic activity.	[16]
12.	Curbilene phytosome	Curbilene from *Curcurbita pepo* seeds	-	Skin care, Matting Agent.	[42]
13.	Bilberry Phytosome	Anthocyanosides from *Vaccinium myrtillus.*	-	Antioxidant, Improvement of Capillary Tone.	[43]
14	Greenselect phytosome	Polyphenols, catechins	320 mg	Management of weight, blood lipids, inflammation and antioxidant capacity.	[44]
15.	Grape seed (Leucoselect) phytosome	Procyanidins from *Vitis vinifera*.	50-300 mg	Nutraceutical, Antioxidant, Anticancer.	[45]
16.	Ginseng phytosome	Ginsenosides from *Panax ginseng*.	150 mg	Nutraceutical, Immunomodulator.	[46]
17.	*Acorus calamus*	Asarone	-	Improve memory power and intellect.	[4]
18.	*Centella asiatica*	Asiaticoside, centelloside, madecassoside, Asiatic acid.	-	Brain tonic, cognition and antianxietyBrain tonic, Vein and Skin Disorder.	[5]
19.	*Corydalis temata*	Protopine	-	Anticholinesterase and amnesic properties.	[6]
20.	Curcumin (Merinoselect) Phytosomes	Curcumin Polyphenol from *Curcuma Longa.*	200-300 m	Prevention of cancer chemotherapy Increased curcuminoids' oral bioavailability and plasma levels.	[6]
21.	*Emblica officinalis*	Vit. C, phyllembin	-	Anticholinesterase activity	[7]

22.	*Evolvulus alsinoides*	Betaine, sankhpushpine and evolvine	-	Memory enhancing agent, used in treatment of dementia.	[8]
23.	Ginkgo select phytosome	Bilobalide, ginkgolides, kaempferol, Flavonoids from *Ginkgo biloba.*	120 mg	Anti-aging, protects brain and vascular tissue and enhances cognitive function.	[9]
24.	*Glycerrhiza glabra*	Glycyrrhizin	-	Effective on improvement in learning and memory in case of scopolamine induced neurodisorders.	[10]
25.	*Rubia cardifolia* L.	Anthraquinone, flavonoid, saponine	-	Anticancer, Immunomodulatory, Antioxidant, hepatoprotective, Anti-inflammatory.	[18]
26	Garlic *Allium sativum*	Allicin	-	Protect from gastric acid.	[20]
27	*Curcuma longa*	Curcumin	8 g/day	Cancer, osteoarthritic, inflammatory effect.	[21]
28	*Echinacea*	Chicoric acid and chlorogenic acid.	-	Antioxidant	[24]
29	Sinigrin phytosome	Sinigrin	-	Cytotoxic effect, anti-inflammatory activity.	[25]
30	*Boswellia*	Boswellic acid.	-	Anti-inflammatory	[28]
31	*Cuminum cyminum* L.	Cumin essential oil	-	Neutraceuticals, natural antioxidant.	[29]
32	*Allium sativum* L.	Allicin	-	Food Preservative, Antibacterials	[47]
33	*Cranberries*(*Vaccinium macrocarpon*)	Anthrocynin, flavan 3 ol, flavonols	-	Colonic microbiota in human, feacal microbial activity.	[31]
34	*Glycyrrhiza*	18B-glycyrrhetinic acid	-	Cosmetic, skin application.	[32]
35	sinigrin	glucosinolates	-	Cytotoxic effect, wound healing.	[33]
36	*Bombax ceiba*	B-sitosterol, Lupeol	-	Hepatoprotectiver, Diebetes.	[34]
37	*Swertia perennis*	Quercetin, flavonoid	-	Antioxidant	[35]
38	*Camellia sinensis*	Gallic acid, catechin, Galocatechin	-	Skin aging	[36]
39	*Piper longa* and *Abutilon indicum*	Quercetin	-	Hepatoprotective	[37]

molecule. Various advance phytosome preparation mention in Table 2.[19]

Phytosome technology possesses several benefits, including the following

1. Phosphatidylcholine, which is a component of phytosome, plays a dual function by acting as a carrier and exerting a hepatoprotective effect.
2. The phytosome composition is deemed to be safe, with its components having received approval for pharmaceutical applications.[38]
3. The absorption and bioavailability of phytoconstituents that are soluble in water are enhanced. Therefore, this leads to enhanced therapeutic outcomes.
4. Phytosomes possess the capability to undergo transition from a hydrophilic environment to a lipophilic environment within enterocyte cells, hence enabling their utilization for systematic targeting purposes.[39]
5. The reduction in dose need is attributed to the enhanced absorption of key phytoconstituents.
6. In contrast to liposomes, phytosomes exhibit enhanced stability due to the formation of chemical interactions between phosphatidylcholine and phytoconstituent.
7. The preservation of nutritional safety in herbal extracts can be maintained without compromising the delivery of herbal therapy by the utilization of phytosomes.[40]
8. The dosage requirement has been reduced due to the efficient absorption of the key constituents.

Table 2: Recent Advances in Phytosome.

Sl. No.	Year	Author	Invention	Objectives	References
1.	2018	Simona Mancini *et al.*	Functionalized liposomes and phytosomes loading *Annona muricata* L. aqueous extract: Phenolic chemical nano-shuttles for brain transport.	Phospholipid nano-formulations of liposomes and phytosomes with peptide ligands protected this extract against gastrointestinal biotransformation and increased BBB permeability. Best phytosomes bound inhibited and scavenged enzymes.	[7]
2.	2020	N. Palachai *et al.*	Metabolic Syndrome Rats Protected against Cerebral Ischemia by Phytosome Mulberry and Ginger Extract loading.	Mulberry fruit and ginger help brain and MetS-related disorders and Phytosomes with the combined extract (PMG) are neuroprotective against ischemic stroke in MetS patients due to the synergistic idea. The first pass impact diminishes polyphenol availability. To reduce brain edema and inflammation, increase PPARγ expression and decrease DNMT.	[48]
3.	2020	Zhiguang Huang *et al.*	Production and comparison of milk phospholipid complexed vitamin C and E antioxidant phytosomes to liposomes.	Dietary phytosome research is rare. Milk phospholipid assemblies were examined for digestion and bioavailability of encapsulated nutrients (ascorbic acid and α-tocopherol) *in vitro*. Ethanolic evaporation produced phytosomes. According to spectral investigations, polar phospholipids connected hydrogen to ascorbic acid hydroxyl groups. Increasing ascorbic acid or α-tocopherol in the assembly altered the complexes' chemical structure.	[49]
4.	2021	Sudhir Kumar *et al.*	Based on *in vitro* antioxidant test, *ex vivo* phytosome study of taxifolin-rich fraction of *Cedrus deodara* bark extract on human breast cancer cell lines.	Taxifolin's cytotoxic action is boosted by lipid-compatible phytocellular vesicles crossing cell lines' outer layer. Phytosome formulations for disease treatment can employ phenolic leaders like taxifolin from ethyl acetate fraction.	[50]
5.	2021	Mohamad Taleuzzaman, *et al.*	Quality by Design core composite design enhanced Manjistha Extract phytosomal gel (MJE).	Formulation was traditional. Improved phytosomal formulation release *in vitro*. Egg membrane flux and penetration were better with phytosomal gel than MJE extract-based gel.	[51]
6.	2022	N. Ninning *et al.*	Synthesis and characterization of enteric-coated delayed-release phytosome-loaded allicin-rich extract microspheres.	Garlic has a natural organosulfur component with several health advantages. Deactivation of alliinase may cause allicin instability in acidic conditions. Thus, delayed-release stomach preparations are needed for optimum absorption. This study creates and analyzes an enteric-coated microsphere with an allicin-rich phytosome-loaded extract to protect against stomach acid.	[52]

Table 3: Evaluation parameter of phytosome .

Parameter	Procedure	References
Solubility Study	Prepare phytosome solution was agitated for 24 hours on rotator shaker then centrifuged for 15 minutes to remove excessive extract. The supernatant was filtered and then 1 ml of filtrate was mixed with 9 ml of methanol to prepare dilutions and measured absorbance at wavelength of 271 nm by UV spectrophotometer.	[53]
Particle size analysis and zeta potential	It can be measured by using dynamic light scattering and photon correlation spectroscopy. Typically, particle sizes range from 50 nm to 100μm.	[54]
Drug Entrapment Efficiency	100 mg of pure extract in methanol. Extract was centrifuged for 40 min at 24°C to separate the drug in the supernatant from the drug incorporated in the phytosomes. Concentrations of extract in the supernatant were determined by UV-visible spectrometry at 271nm.	[55]
Differential Scanning Colorimetry	The transition temperature can be determined by differential scanning calorimetry (DSC-Mettler Toledo), 2 mg of the sample in the aluminum pans and heated at the 5oC /min, a temperature range of 20oC to 300oC under nitrogen atmosphere of flow rate 30ml/min	[53]
Drug-excipient compatibility studies	The lyophilized sample treated with dry crystalline KBr (1:100) to prepare circular transparent discs on compression under the pressure of 10 Ton/nm2. Each KBr disc was scanned at 4 mm/s at a resolution of 2 cm− 1 and the spectrum was observed for each sample within the wave number region of 4000–400 cm− 1.	[56]
Stability study	The formulations were sealed in glass vials and stored at a temperature of 4 ± 0.5 °C and a relative humidity (RH) of 75 ± 5%. Analysis of various parameters of the prepare formulation was performed at the initial stage, as well as at the third and sixth months of the stability study.	[57]
In vitro drug release study	Phytosomes was taken into 900 mL of 0.1 N HCl, pH 1.2, maintained at a temperature of 37°C ± 0.5°C and stirred at a speed of 50 rpm. At different time intervals, a 5 ml of the sample was withdrawn and sink condition they can maintained. After 2 hrs. same procedure was repeated. The collected samples were filtered using Whatman filter paper and analyzed at λ-max 288 nm using a UV-Visible spectrophotometer against 0.1N HCl and phosphate buffer 6.8 pH as blank.	[58]

9. The medicine exhibits a notable enhancement in its bioavailability.
10. The entrapment efficiency of the medication is significantly elevated and predetermined as a result of its conjugation with lipids during the process of vesicle formation.
11. No issues have been discovered in drug entrapment during the formulation of phytosomes.
12. The improved stability properties of phytosomes can be attributed to the development of chemical connections between molecules of phosphatidylcholine and the phytoconstituents.
13. Phosphatidylcholine, an essential component in the phytosome process, functions as a transporter and nourishing agent for the skin owing to its crucial involvement in the composition of cell membranes.
14. When incorporated into skincare formulas, phytosomes demonstrate a greater level of effectiveness in comparison to liposomes.
15. The safety of the formulation and ingredients utilized in the synthesis of phytosomes has been established, making them appropriate for use in commercial applications. Moreover, it is important to highlight that this specific technology demonstrates a low level of risk, as the toxicity evaluations conducted on its many constituents have been thoroughly documented.
16. The utilization of phytosomes has been observed to possess advantageous properties in the sustenance and conservation of hepatic functionality. In addition, phosphatidylcholine has a crucial role in improving the absorption of flavonoids, which are vital for the maintenance of good hepatic function. Moreover, phosphatidylcholine exhibits defensive attributes that help to the general health of the liver.[41]
17. Phytosomes present a cost-efficient approach for administering phytoconstituents that possess skin-protective attributes in diverse environmental circumstances, including both typical and challenging environments. The significance of phosphatidylcholine in the preservation of skin health is of utmost importance as it facilitates the delivery of vital nutrients. In addition, phytosomes have been found

to improve the distribution of phytoconstituents that are produced via dermal and transdermal routes. The results of the investigation revealed that the curcumin phytosome demonstrated a penetration rate that was 60% greater.

18. Phytosome technology represents a passive and non-invasive methodology that presents the advantage of improved bioavailability and is now accessible inside the commercial sphere.
19. The phenomenon of drug entrapment does not manifest itself throughout the formulation process.
20. Phytosomes present a promising strategy for the delivery of a wide range of medicinal substances, accompanied by improved stability due to the chemical interaction between the phospholipid and the therapeutic agents.
21. The potential reduction of the effective dosage may be attributed to the improved bioavailability and absorption of the phytoconstituent, along with the prolonged release pattern demonstrated by the phytosome. To put it otherwise, the administration of a reduced amount of the phytoconstituent may still result in the intended outcome.
22. The process of synthesizing phytosomes is characterized by a reasonably uncomplicated approach, hence necessitating only little technical proficiency and financial means.
23. Phytosomes exhibit a notable level of efficacy and efficiency in transitioning from a hydrophilic milieu to a hydrophobic milieu, particularly the enterocyte membrane and subsequently accessing the cellular compartment. Consequently, they can be utilized for the objective of systematic targeting.
24. The incorporation of phospholipids contributes to the augmentation of the nutritional content of the plant extract.
25. The methodology for the preparation of Phytosome is relatively uncomplicated.
26. The phytosome exhibits a notable capacity for efficient transdermal absorption.
27. The existence of a phospholipid layer aids in the protection of water-soluble phytoconstituents against degradation caused by digestive enzymes and gut bacteria.
28. The application of phytosomes offers a feasible strategy for attaining systematic targeting.
29. The large-scale creation of medications has minimal risk due to the extensively established toxicological profile of the phytosomal component, as supported by scholarly literature.
30. The development of phytosome is a straightforward process that does not necessitate substantial technical expenditure.

Disadvantages

Despite the manifold benefits associated with Phytosome technology, it is imperative to realize that this methodology also entails certain limitations, notably the rapid depletion of phytoconstituents from the Phytosomes.

CONCLUSION

The phytosome is an innovative formulation for herbal extracts that demonstrates superior absorption in comparison to conventional herbal extracts. The issue of restricted bioavailability and absorption of water-soluble phytoconstituents can be effectively resolved by the application of phytosome technology. This innovative approach enables the efficient delivery of active phytoconstituents, hence enhancing their effectiveness. Phytosomes have enhanced absorption characteristics due to their increased lipid solubility, which enables their efficient permeation through biological membranes. This property allows for improved bioavailability since phytosomes may be effectively absorbed through both the skin and gastrointestinal system. The increased bioavailability of the product leads to a decreased frequency of dosing needed in comparison to conventional herbal extracts. There are further facets of phytosomes that necessitate further exploration in forthcoming research, particularly with regards to their prospective utility within the pharmacological domain. Phytosome technology is a sophisticated method for administering herbal extracts or phytochemicals, distinguished by its ability to improve the absorption of drugs and boost therapeutic effectiveness.

ACKNOWLEDGEMENT

The authors are thankful to DST, Delhi and RGSTC, Mumbai for research project funding for Alzheimer's disease.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

REFERENCES

1. Murugesan MP, Venkata Ratnam MV, Mengitsu Y, Kandasamy K. Evaluation of anti-cancer activity of phytosomes formulated from Aloe vera extract. Mater Today Proc. 2021;42:631-6. doi: 10.1016/j.matpr.2020.11.047.
2. Khogta S, Patel J, Barve K, Londhe V. Herbal nano-formulations for topical delivery. J Herb Med. 2020;20:100300. doi: 10.1016/j.hermed.2019.100300.
3. Djekic L, Krajišnik D, Mićic Z, Čalija B. Formulation and physicochemical characterization of hydrogels with 18β-glycyrrhetinic acid/phospholipid complex phytosomes. J Drug Deliv Sci Technol. 2016;35:81-90. doi: 10.1016/j.jddst.2016.06.008.
4. McGuckin MB, Wang J, Ghanma R, Qin N, Palma SD, Donnelly RF, *et al.* Nanocrystals as a master key to deliver hydrophobic drugs via multiple administration routes. J Control Release. 2022;345:334-53. doi: 10.1016/j.jconrel.2022.03.012, PMID 35283257.
5. Maryana W, Rachmawati H, Mudhakir D. Formation of phytosome containing silymarin using thin layer-hydration technique aimed for oral delivery. Mater Today Proc. 2016;3(3):855-66. doi: 10.1016/j.matpr.2016.02.019.
6. Panda VS, Naik SR. Cardioprotective activity of Ginkgo biloba phytosomes in isoproterenol-induced myocardial necrosis in rats: a biochemical and histoarchitectural evaluation. Exp Toxicol Pathol. 2008;60(4-5):397-404. doi: 10.1016/j.etp.2008.03.010, PMID 18513933.

7. Mancini S, Nardo L, Gregori M, Ribeiro I, Mantegazza F, Delerue-Matos C, *et al.* Functionalized liposomes and phytosomes loading *Annona muricata* L. aqueous extract: potential nanoshuttles for brain-delivery of phenolic compounds. Phytomedicine. 2018;42:233-44. doi: 10.1016/j.phymed.2018.03.053, PMID 29655691.
8. Singh RP, Gangadharappa HV, Mruthunjaya K. Phytosome complexed with chitosan for gingerol delivery in the treatment of respiratory infection: *in vitro* and *in vivo* evaluation. Eur J Pharm Sci. 2018;122:214-29. doi: 10.1016/j.ejps.2018.06.028, PMID 29966737.
9. Mehta P, Bothiraja C, Mahadik K, Kadam S, Pawar A. Phytoconstituent based dry powder inhalers as biomedicine for the management of pulmonary diseases. Biomed Pharmacother. 2018;108:828-37. doi: 10.1016/j.biopha.2018.09.094, PMID 30372894.
10. Kumar S, Baldi A, Sharma DK. *In vitro* antioxidant assay guided *ex vivo* investigation of cytotoxic effect of phytosomes assimilating taxifolin rich fraction of Cedrus deodara bark extract on human breast cancer cell lines (mcf7). J Drug Deliv Sci Technol. 2021;63:102486. doi: 10.1016/j.jddst.2021.102486.
11. Pande SD, Wagh AS, Bhagure LB, Patil SG, Deshmukh AR. Preparation and evaluation of phytosomes of Pomegrane peels. Res J Pharm Technol. 2015;8(4):416. doi: 10.5958/0974-360X.2015.00070.0.
12. Shalini S, Kumar RR, Birendra S. *Terminalia arjuna* bark on Human Breast Cancer Cell Lines (MCF-7). Int J Drug Dev Res,. 2015;7(1):9344: 0975.
13. Sasongko RE, Surini S, Saputri FC. Formulation and characterization of bitter melon extract (*Momordica charantia*) loaded phytosomes. Pharmacogn J. 2019;11(6):1235-41. doi: 10.5530/pj.2019.11.192.
14. Ittadwar PA, Puranik PK. Novel umbelliferone phytosomes: development and optimization using experimental design approach and evaluation of photo-protective and antioxidant activity. Int J Pharm Pharm Sci. 2017;9:218-28.
15. Kalita B, Das MK. Resveratrol-phospholipid complexes (phytosomes) with improved physicochemical properties favorable for drug delivery via skin. World J Pharm Res. 2015;4(5):1497-517.
16. Amudha S, Prabal KM, Jeganathan NS. Evaluation of antidiabetic activity of *Syzygium cumini* extract and its phytosome formulation against streptozotocin-induced diabetic rats. Pharm Innov J. 2018;7:603-8.
17. Direito R, Reis C, Roque L, Gonçalves M, Sanches-Silva A, Gaspar MM, *et al.* Phytosomes with persimmon (*Diospyros kaki* L.) extract: preparation and preliminary demonstration of *in vivo* tolerability. Pharmaceutics. 2019;11(6):296. doi: 10.3390/pharmaceutics11060296, PMID 31234548.
18. Taleuzzaman M, Sartaj A, Kumar Gupta D, Gilani SJ, Mirza MA. Phytosomal gel of Manjistha extract (MJE) formulated and optimized with central composite design of Quality by Design (QbD). J Dispers Sci Technol. 2021:1-9.
19. Joshi G, Tiwari A, Upadhyay P. Development and characterization of herbosomes complex. J Pharm Res. 2020;10(06).
20. NINING N, SRIFIANA Y, FADLIANTY EM. Preparation and characterization of enteric-coated delayed-release microsphere of phytosome loading allicin-rich extract. Int J Appl Pharm. 2021:71-5. doi: 10.22159/ijap.2021.v13s3.15.
21. Ghanbarzadeh B, Babazadeh A, Hamishehkar H. Nano-phytosome as a potential food-grade delivery system. Food Biosci. 2016;15:126-35. doi: 10.1016/j.fbio.2016.07.006.
22. Habbu P, Madagundi S, Kulkarni R, Jadav S, Vanakudri R, Kulkarni V. Preparation and evaluation of Bacopa-phospholipid complex for antiamnesic activity in rodents. Drug Invent Today. 2013;5(1):13-21. doi: 10.1016/j.dit.2013.02.004.
23. Basu SK, Thomas JE, Acharya SN. Prospects for growth in global nutraceutical and functional food markets: a Canadian perspective. Aust J Basic Appl Sci. 2007;1(4):637-49.
24. Molaveisi M, Shahidi Noghabi MS, Parastouei K, Taheri RA. Fate of nano-phytosomes containing bioactive compounds of Echinacea extract in an acidic food beverage. Food Struct. 2021;27:100177. doi: 10.1016/j.foostr.2021.100177.
25. Saeed M, Sadr S, Gharib A, Lotfalizadeh N, Hajjafari A, Ahmadi Simab PA, *et al.* Phytosomes: A promising nanocarrier for enhanced delivery of herbal compounds in cancer therapy. J Lab Anim Res. 2022;1(1):26-32. doi: 10.58803/jlar.v1i1.8.
26. Mazumder A, Dwivedi A, Du Preez JL, Du Plessis J. *In vitro* wound healing and cytotoxic effects of sinigrin-phytosome complex. Int J Pharm. 2016;498(1-2):283-93. doi: 10.1016/j.ijpharm.2015.12.027, PMID 26706438.
27. Caicedo Chacon WD, Verruck S, Monteiro AR, Valencia GA. The mechanism, biopolymers and active compounds for the production of nanoparticles by anti-solvent precipitation: a review. Food Res Int. 2023;168:112728. doi: 10.1016/j.foodres.2023.112728, PMID 37120194.
28. Hüsch J, Bohnet J, Fricker G, Skarke C, Artaria C, Appendino G, *et al.* Enhanced absorption of boswellic acids by a lecithin delivery form (Phytosome®) of Boswellia extract. Fitoterapia. 2013;84:89-98. doi: 10.1016/j.fitote.2012.10.002, PMID 23092618.
29. Khosh manzar M, Mohammadi M, Hamishehkar H, Piruzifard MK. Nanophytosome as a promising carrier for improving cumin essential oil properties. Food Biosci. 2021;42:101079. doi: 10.1016/j.fbio.2021.101079.
30. Nazari M, Ghanbarzadeh B, Samadi Kafil HS, Zeinali M, Hamishehkar H. Garlic essential oil nanophytosomes as a natural food preservative: its application in yogurt as food model. Colloids Interface Sci Commun. 2019;30:100176. doi: 10.1016/j.colcom.2019.100176.
31. Bresciani L, Di Pede G, Favari C, Calani L, Francinelli V, Riva A, et al. *In vitro* (poly) phenol catabolism of unformulated- and phytosome-formulated cranberry (*Vaccinium macrocarpon*) extracts. Food Res Int. 2021;141:110137. doi: 10.1016/j.foodres.2021.110137.
32. Djekic L, Krajišnik D, Mićic Z, Čalija B. Formulation and physicochemical characterization of hydrogels with 18β-glycyrrhetinic acid/phospholipid complex phytosomes. J Drug Deliv Sci Technol. 2016;35:81-90. doi: 10.1016/j.jddst.2016.06.008.
33. Dutt Y, Pandey RP, Dutt M, Gupta A, Vibhuti A, Raj VS, *et al.* Liposomes and phytosomes: nanocarrier systems and their applications for the delivery of phytoconstituents. Coord Chem Rev. 2023;491:215251. doi: 10.1016/j.ccr.2023.215251.
34. Karole S, Gupta GK. Preparation and evaluation of phytosomes containing ethanolic extract of leaves of *Bombax ceiba* for hepatoprotective activity. Evaluation. 2019;6(2):1-5.
35. Chouhan A, Shah SK, Tyagi CK, Budholiya P, Wazid A, Khan F. Formulation, development and evaluation of phytosomes of *Swertia perennis*. AJPER JOURNAL. 2021;10(2):55-66. doi: 10.38164/AJPER/10.2.2021.55-66.
36. Bharati R, Badola A. Formulation and evaluation of phytosomal gel of *Camellia sinensis* for treatment of skin ageing; 2021.
37. Sharma S, Sahu AN. Development, characterization and evaluation of hepatoprotective effect of *Abutilon indicum* and *Piper longum* phytosomes. Pharmacogn Res. 2016;8(1):29-36. doi: 10.4103/0974-8490.171102, PMID 26941533.
38. Riva A, Ronchi M, Petrangolini G, Bosisio S, Allegrini P. Improved oral absorption of quercetin from quercetin phytosome®, a new delivery system based on food grade lecithin. Eur J Drug Metab Pharmacokinet. 2019;44(2):169-77. doi: 10.1007/s13318-018-0517-3, PMID 30328058.
39. Pereira A, Mallya R. Formulation and evaluation of a photoprotectant cream containing *Phyllanthus emblica* extract-phospholipid complex. J Pharmacogn Phytochem. 2015;4(2).
40. Maryana W, Rachmawati H, Mudhakir D. Formation of phytosome containing silymarin using thin layer-hydration technique aimed for oral delivery. Mater Today Proc. 2016;3(3):855-66. doi: 10.1016/j.matpr.2016.02.019.
41. Priani SE, Aprilia S, Aryani R, Purwanti L. Antioxidant and tyrosinase inhibitory activity of face serum containing cocoa pod husk phytosome (*Theobroma cacao* L.). J App Pharm Sci. 2019;9(10):110-5. doi: 10.7324/JAPS.2019.91015.
42. Karimi N, Ghanbarzadeh B, Hamishehkar H, Pezeshki A, Mostafayi H, Gholian MM. Phytosome as novel delivery system for nutraceutical materials. Int J Curr Microbiol Appl Sci. 2015;4(6):152-9.
43. Amin T, Bhat SV. A review on phytosome technology as a novel approach to improve the bioavailability of nutraceuticals. Int J Adv Res Technol. 2012;1(3):1-5.
44. Belcaro G, Ledda A, Hu S, Cesarone MR, Feragalli B, Dugall M. Greenselect phytosome for borderline metabolic syndrome. Evid Based Complement Alternat Med. 2013;2013:869061. doi: 10.1155/2013/869061, PMID 24348726.
45. Nuttall SL, Kendall MJ, Bombardelli E, Morazzoni P. An evaluation of the antioxidant activity of a standardized grape seed extract, Leucoselect®. J Clin Pharm Ther. 1998;23(5):385-9. doi: 10.1046/j.1365-2710.1998.00180.x, PMID 9875688.
46. Kumar N, Goel R, Gaur PK, Saxena PK, Puri D, Chaudhary R, *et al.* Development and evaluation of phytosome-loaded microsphere system for delivery of ginseng extract. J Microencapsul. 2021;38(7-8):496-506. doi: 10.1080/02652048.2021.1982042, PMID 34529549.
47. Shang A, Cao SY, Xu XY, Gan RY, Tang GY, Corke H, *et al.* Bioactive compounds and biological functions of garlic (*Allium sativum* L.). Foods. 2019;8(7):246. doi: 10.3390/foods8070246, PMID 31284512.
48. Wattanathorn J, Palachai N, Thukham-Mee W, Muchimapura S. Memory-enhancing effect of a phytosome containing the combined extract of mulberry fruit and ginger in an animal model of ischemic stroke with metabolic syndrome. Oxid Med Cell Longev. 2020; 2020:3096826. doi: 10.1155/2020/3096826, PMID 32802263.
49. Huang Z, Brennan CS, Zhao H, Liu J, Guan W, Mohan MS, *et al.* Fabrication and assessment of milk phospholipid-complexed antioxidant phytosomes with vitamin C and E: A comparison with liposomes. Food Chem. 2020;324:126837. doi: 10.1016/j.foodchem.2020.126837, PMID 32339791.
50. Kumar S, Baldi A, Sharma DK. *In vitro* antioxidant assay guided *ex vivo* investigation of cytotoxic effect of phytosomes assimilating taxifolin rich fraction of *Cedrus deodara* bark extract on human breast cancer cell lines (mcf7). J Drug Deliv Sci Technol. 2021;63:102486. doi: 10.1016/j.jddst.2021.102486.
51. Verma S, Tonk RK, Albratty M, Alhazmi HA, Najmi A, Kumar R, *et al.* Design and evaluation of sustained release mucoadhesive film of sumatriptan succinate containing grafted co-polymer as the platform. Saudi Pharm J. 2022;30(11):1527-37. doi: 10.1016/j.jsps.2022.07.014, PMID 36465843.
52. NINING N, SRIFIANA Y, FADLIANTY EM. Preparation and characterization of enteric-coated delayed-release microsphere of phytosome loading allicin-rich extract. Int J Appl Pharm. 2021:71-5. doi: 10.22159/ijap.2021.v13s3.15.

Cite this article: Vighne RC, Deore SL, Baviskar BA. A Comparative Investigation on the Phytosomes of Diverse Bioactive Nootropic Medicinal Herbs. Pharmacog Rev. 2024;18(36):117-26.