Chapter

Phytosomes as a Novel Approach to Drug Delivery System

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Abstract

"Phyto" refers to a plant, whereas "some" refers to something that looks like a cell. The other term for it is herbosomes. This is a brand-new, patented technique that mixes phospholipids with systematic herbal extracts or moisture phytocomponents to produce lipid-consistent tiny composites that significantly increase absorption and bioavailability. Phosphatidylcholine, phosphatidylinositol, phosphatidylserine, and phosphatidylethanolamine are frequently used phospholipids. Plant-derived therapies have gained notoriety and acceptance in the worldwide drug trade as safe and effective alternatives to contemporary synthetic medications as a result of their complex and unpleasant interactions. According to World Health Organization (WHO), more than 80% of people around the world believe in herbal remedies. Active ingredients originating from plants have been used to treat a number of diseases since the dawn of time. Natural plant extracts that are active have been proven to have strong pharmacological effects *in vitro* but limited *in vivo* absorption. Poor absorption has been addressed in a number of ways, including the creation of emulsions, liposomes, and nanoparticles, as well as the alteration of chemical structures and administration as prodrugs. Phytophospholipid complexes, also known as phytosomes, have emerged as a promising tactic to increase the bioavailability of active ingredients among the possible approaches.

Keywords: phytosome, bioavailability, solubility, effects, novel drug delivery, phosphatidylcholine

1. Introduction

A new method of administering medication that gets over the drawbacks of conventional approaches is known as a unique drug delivery system [1, 2]. The vast body of Ayurvedic knowledge that exists in our nation has only recently been recognized for its potential. On the other hand, the patient's prior administration of herbaceous medications was done through an obsolete and inadequate medication delivery system, which lowered the drug's potency. Innovative medication parturition techniques may even increase the efficacy of certain botanical components and medicines while reducing associated adverse effects in herbaceous remedies. This fundamental idea serves as the foundation for the inclusion of a distinctive method of drug administration in herbal therapies. Several herbs, notably those with polyphenolic rings in their frames, such

as flavonoids, terpenoids, and coumarins, have been shown to have a base oral bioaccumulation. Many active ingredients derived from plants, on the other hand, are poorly absorbed when taken by mouth, limiting their use. These chemicals have a low absorption rate due to two factors. Polyphenols' multi-ring structures are too big for passive diffusion or non-active absorption. Second, the low solubility of these chemicals in water or lipids prevents them from getting through the gastrointestinal cells' outer membrane.

Active compounds extracted from plant sources have been shown to have therapeutic effects *in vitro*, but *in vivo* absorption is often minimal. A variety of solutions have been proposed to address the issue of poor absorption, such as the development of emulsions, liposomes, and nanoparticles, as well as chemical structure modification and distribution as prodrugs. Phytophospholipid complexes, sometimes referred to as phytosomes, have developed into a crucial method for increasing the bioavailability of active ingredients.

2. Phytosomes or phytophospholipid complexes or herbosomes

"Phyto" refers to a plant, whereas "some" refers to something that looks like a cell [2–4]. Herbosome is the other name for it. This is the novel approach to drug delivery system that combines biologically active phytoconstituents of herbal extracts surrounded and bound by phospholipids. By treating plant extracts, ginseng, flavonoids, etc., phytosome technology improves the bioavailability, lipid solubility, and stability of herbal extract. Phytophospholipid complexes called phytosomes are created by combining phytoconstituents with lipid-compatible phospholipids. Phospholipids, such as soy lecithin components like phosphotidylcholine, phosphotidylethanolamine, and phosphotidylserine, are used in the creation of phytosomes.

Active ingredients are complexed at precise mole ratio with phospholipids (phosphatidylcholine) under certain conditions to produce phytophospholipid complexes. The choline fraction is hygrophilous, and the phosphatidyl fraction is hydrophobic, making phosphatidylcholine a bifunctional molecule. The choline lead about the phosphatidylcholine speck attaches to the photosensitive ingredient in the phytophospholipid complex, while the lipid-soluble section wraps around it. As a result, phytophospholipid complex is produced (**Figure 1**).

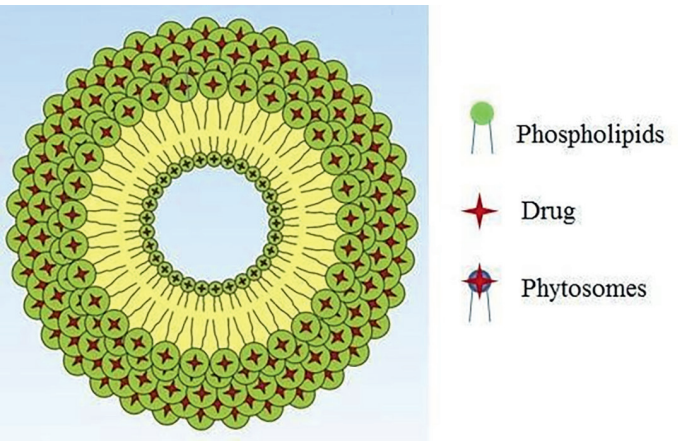

Figure 1.
Structure of phytosome-loaded complex [4].

2.1 Components of phytosomes

There are three main components of phytosomes [5, 6]:

a. Phospholipids

b. Active phytoconstituents

c. Solvents

2.1.1 Phospholipids

Both cellular and sub-cellular membranes include phospholipids. Humans, animals, and plants all have them. A polar head and nonpolar acyl chains that are once more connected to alcohol make up phospholipids. There are many phospholipids present as a result of differences in hydrophilic groups, aliphatic chains, and alcohols. Examples of phospholipids found in eukaryotic cell membranes include phosphatidylcholine, cardiolipin, phosphatidylethanolamine, phosphatidylserine, sphingolipids, and phosphatidylinositol 7. Many various types of formulations use phospholipids, including natural, synthesized, and hydrogenated phospholipids such as soy lecithin components like phosphatidylcholine.

Relying on their backbone, phospholipids are classified as glycerophospholipids or sphingomyelins. Phosphatidylcholine (PC), phosphatidylethanolamine (PE), phosphatidylserine (PS), phosphatidic acid (PA), phosphatidylinositol (PI), and phosphatidylglycerol (PG) are all examples of glycerophospholipids (PG). The main phospholipids utilized to make complexes with a hydrophilic head group and two hydrophobic hydrocarbon chains are PC, PE, and PS. Phospholipid complexes are most often made with phosphatidylcholine, which is the most widespread phospholipid. The amphipathic features of phosphatidylcholine offer it moderate solubility in both water and lipid mediums, which is one of its advantages. Furthermore, because phosphatidylcholine is a necessary component of cell membranes, it has a high level of biocompatibility and is low in toxicity. Hepato-protective properties of phosphatidylcholine molecules have been observed in the remedy of liver-colored illnesses such as "hepatitis, fatty liver, and hepatocirrhosis".

2.1.2 Active phytoconstituents

Flavonoids make up a large portion of phytomedicines' bioactive components (e.g., milk bramble contains silymarin, bilberry has anthocyanidins, and green tea comprises catechins). The majority of flavonoids, however, are poorly absorbed. Phytosomes are generated from standardized plant extracts, primarily flavonoids. Flavonoids are chosen from a category that includes "quercetin, kaempferol, quercretin-3, rhamnoglucoside, quercetin-3-rhamnoside, hyperoside, vitexine, diosmine, 3-rhamnoside, (+) catechin, (-) epicatechin, apigenin-7-glucoside, luteolin, luteolin-glucoside, ginkgetin, isogink".

2.1.3 Solvents

In the preparation of phytosomes, the phospholipids are mixed with inorganic solvents; phytosomes are prepared by a one solvent or mixed solvent system. Though

several publications have utilized mixed solvent systems in which the phospholipids are dissolved in a separate solvent than the drug/extract, for example, aprotic solvent—tetrahydrofuran, dichloromethane, diethyl ether and chloroform, protic solvents—ethanol, even though typical preparation procedures use a single solvent. More subsequently, protonic solvents including ethanol and methanol have been used to make phospholipid aggregates.

2.2 Characteristics of phytosomes

2.2.1 Chemical properties

Phytocomplexes are prepared as a result of a reaction between substrate and polymer (phospholipids) generally in ratios 1:1 and 1:2 or based on the essential quantity of phospholipids and substrate. There is evidence of the establishment of hydrogen bonding during the time when both parties were in contact, in the polar regions of both phospholipids and substrate molecules. It is possible to investigate it using a spectroscopic apparatus. While phytosomes are linked to the phospholipids' glacial surface, they can transform into a portion of the molecular film's interior where OH bonds with the phenol hydroxyls of the flavone moiety can be formed. As long as the signals from the fatty sequence are largely unaffected, it is possible to make the NMR of the phytosomes more similar to that of the unaltered precursor, which would demonstrate the phytosomes' accessibility through the evaluation of substance properties.

2.2.2 Biological properties

Phytosomes are the sophisticated as a natural world for herbal crops with the aim of these products making the superior absorption and consumption as improved domino effect over the entire predictable herbal drugs 10. Phytosome is helpful to build the bioavailability of the phytosomes rather than the non-complexes botanical herbs. It has been established as a result of *in vitro* and *in vivo* studies for better invention of herbs in living thing.

2.3 Application

Phytosomes have the following benefits over conventional medicinal herbs [7–10]:

1. *Enhancing bioavailability:*

The quinoline alkaloid evodiamine (*Evodia rutaecarpa*) has a wide range of pharmacological effects. Improved *in vitro* dissolving rate, greater absorption, longer action time, and improved bioavailability were all demonstrated by Phytosomes of Evodiamine. A prolonged action time and higher bioavailability were observed due to the extended release of the drug from the phytosomes. Moreover, these phytosomes might reduce the first-pass metabolism of Evodiamine by bypassing liver and therefore avoiding the direct contact of the drug with the hepatic metabolism enzymes. The bioavailability and $T_{1/2}$ of Evodiamine was 1772.35 μg h^{-1} L^{-1} and 1.33 hours, respectively. The enhanced bioavailability and T1/2 with phytosomes were 3787.24 μg h^{-1} L^{-1} and 2.07 hours, respectively.

2. *Cancer treatment:*

The primary antioxidant capabilities of medicinal plants' chemical constituents, such as flavones, isoflavones, flavonoids, anthocyanins, coumarins, lignins, catechins, and isocatechins, contribute to their anticancer potential. Some plant-based substances, though, are hazardous at larger doses and have specific adverse effects. The numerous adverse effects of currently accessible, pricey conventional cancer treatments like chemotherapy and radiotherapy, including myelosuppression and neurological, cardiac, pulmonary, and renal toxicity, seriously impair quality of life. These plant-derived medications are trapped inside of a bipolar moiety to increase their solubility, dispersibility, and permeability, which makes them a powerful anti-cancer agent.

Shalini et al. [7] researched on methanolic extract of Terminalia arjuna bark and its phytosome to investigate its antiproliferative activity on human breast cancer cell line MCF-7 by MTT assay by comparing its activities with Quercetin and its phytosomes. The IC50 values of the extract and its phytosome were 25 and 15 μg/ml, respectively, which suggest that they exert more antiproliferative effect as compared to free drug.

3. *Wound healing:*

When Mazumderetal et al. [8] assessed both individually and as a phytosome complex on HaCaT cells, sinigrin, one of the main glucosinolates present in the Brassicaceae plant family, demonstrated wound healing potential. When combined with phytosomes, sinigrin, the wound heals completely (100%) as opposed to the phytoconstituent alone, which only heals 71% of the wound. On the A-375 melanoma cells, sinigrin phytosomes also exhibit improved anticancer activity.

4. *Transdermal application:*

Phytosomes can overcome skin barriers, and are therefore effective carriers for herbal medicines. They are often made by mixing phospholipid molecules with phytoconstituent substances found in extracts from medicinal plants. By increasing the bioavailability and absorption of phytoconstituents like polyphenols, they have enhanced their clinical applications.

5. The key components in herbal extracts are safeguarded by phytosomes, which generate a small cell that protects them from gut bacteria and digestive secretions.

6. It ensures that the active pharmaceutical ingredients are delivered to the appropriate tissues in a timely manner.

7. By delivering the herbal medication as phytosomes, the nutritional safety of the herbal extract does not have to be jeopardized (damage).

8. Because the active component's absorption has enhanced, a tiny dose can provide the desired outcomes.

9. Because the medication is conjugated with lipids in the formation of vesicles, entrapment efficiency is high and greater than predicted.

10. It is simple to construct since drug entrapment is not an issue.

11. Phosphatidylcholine, which is employed in the phytosomes process and is a vital element of a cell membrane, not only acts as a transporter but also nourishes the skin.

12. In skin care products, phytosomes are more effective than liposomes.

13. In aqueous media, they are less soluble, allowing stable emulsions or creams to develop.

2.4 Advantages

Strengthened bioaccumulation:

The phytophospholipid combination enables greater absorption of hydrophilic herbal extracts by allowing them to penetrate the intestinal lumen [4, 5, 8]. When secondary metabolites are complexed with such a lipophilic head of phospholipids, their bioavailability vastly improves.

Synergistic and safe:

Since phosphatidylcholine, which is utilized in complexation, is a crucial aspect of the cell membrane, the additives used in the phytosome formulation have been authorized, making it a safe and secure idea. Because phosphatidylcholine has a hepatoprotective function, it has been demonstrated to have a synergistic impact when complexed with hepatoprotective medicines. In adverse environmental settings, synergistic benefits can be shown in skin protection against exogenous or endogenous toxins. Because of improved absorption of the active ingredient, the phytosomes idea ensures prolonged action duration towards down doses with a reduced venture contour.

Low-risk profile:

As indicated by available data, toxicological consequences are minimal, and manufacturing is limited to a small scale.

Cost efficiency:

This method allows for the delivery of phytoconstituents at a low cost. A neuronal vesicular system is subservient and open to future growth right away. It is quite simple to create phytosomes since no difficult technological expenditure is required and no brings wealth speculation is required.

Transdermal medication administration:

Aromatic phytosomes can also be used to increase medication diffusion through to the peel in transdermal medicament administration since whoever functions as a foretop for a wide variety of medicines, including peptides and proteins.

Perishable:

Phosphatidylcholine, which is used in the formulation of phytosomes, acts as a carrier transporter and is an inherent part of the cell, there is no problem with pharmaceutical plot throughout formation.

Entrapment efficiency is high:

The efficacy of drug entrapment is quite great, and no hazardous metabolites are created. Furthermore, when the biomarker bonds with soybean lipids, it produces nano-cellular vesicles, and medication release may be controlled.

Disadvantage:

Despite the fact that phytosomes have many benefits, they also have some drawbacks, such as the ability of phospholipids (lecithin) to promote the growth of the MCF-7 breast cancer cell line.

Other disadvantage is elimination of phytoconstituents from the phytosomes.

2.5 Preparation

Three main techniques for synthesizing phytophospholipid complexes [9, 11, 12].

a. Solvent evaporation

b. Anhydrous co-solvent lyophilization

c. Anti-solvent precipitation

a. *Solvent evaporation method:*

Dissolve the phytoconstituent and phospholipid separately in a suitable organic solvent, usually chloroform or methanol. Mix the two solutions to attain a specific ratio of phytoconstituent to phospholipid. The solvent is then evaporated under reduced pressure using a rotary evaporator. The obtained complex is further dried to ensure complete removal of solvent and then stored.

Yu et al. used a quick solvent evaporation process followed by a self-assembly methodology to create berberine-phospholipid complexes (P-BER) in order to produce a more efficient berberine drug delivery system.

b. *Anhydrous co-solvent lyophilization:*

A specified quantity of medicine, copolymer, and phospholipids can be immersed in a specific solvent in a rotating cylindrical distillation flask, and then agitated for 3 hours at room temperature not exceeding 40°C. Before adding n-hexane and agitating frequently with a mechanical stirring, a thin covering of the specimen can be achieved. The phytosome-loaded aggregate can be collected and incubated at room temperature in an orangish glass container.

c. *Technique of anti-solvent precipitation:*

A precise quantity of medication, phospholipids, and polymer can be placed in a spherical bottom flask and refluxed for 2 hours with a specific solvent at a temperature of not more than 60°C. A second solvent (referred to as anti-solvent in various reports) is then added to the solution with stirring to obtain the precipitated phospholipid complex. The precipitate can be filtered and dried to obtain the final product.

2.6 Mechanism of phytosomes complex

Phytosomes are often used in the context of improving the solubility and bioavailability of poorly water-soluble phytochemicals or botanical drugs. Phospholipid complexation involves the interaction between the phospholipids and the phytoconstituents. Here is a general mechanism for how it works.

Interaction with the phospholipid bilayer: The primary structure of phospholipids contains a hydrophilic "head" and two hydrophobic "tails". This amphiphilic nature allows phospholipids to form bilayers, with the hydrophilic heads facing outward and the hydrophobic tails tucked inside.

Complex formation: The poorly water-soluble phytochemicals, which are usually lipophilic (fat-loving) or hydrophobic, interact with the hydrophobic region of the phospholipid. This interaction leads to the formation of a complex between the phytoconstituent and the phospholipid.

Enhanced solubility: Due to the amphiphilic nature of phospholipids, the complex's overall solubility in water is enhanced. This is because the outer hydrophilic region of the phospholipid can interact with water, making it easier for the complex to dissolve.

Enhanced permeability: The phytophospholipid complex might alter the permeability of membranes, making it easier for the compound to traverse biological barriers.

The exact mechanism and efficiency can vary based on the specific phytochemical and phospholipid used.

2.7 Characterization of phytosomes

It is important to study the characteristics of phytosomes and their effects [9, 11, 12].

2.7.1 Entrapment efficiency

It is measured by the centrifugation technique. The drug phytosomal complex is centrifuged and the phytosomes are separated from non-entrapped drugs and the drug concentration is usually quantified by ultraviolet spectroscopy. Entrapment efficiency (%) is calculated by using the formula;

$$\text{Percentage} = \frac{\text{Weight of total drug} - \text{weight of free drug}}{\text{Entrapment Weight of total drug}} \times 100 \qquad (1)$$

2.7.2 Zeta potential and particle analysis

Zeta potential is determined by using laser Doppler velocimetry, whereas zeta potential and particle analysis can be determined by various methods but the most commonly used method is by photon correlation spectroscopy and dynamic light scattering.

2.7.3 Spectroscopic assessment

The ^{13}CNMR, 1HNMR, and FT-IR are the spectroscopic techniques used to confirm the lipid-compatible complex of phytosomes.

1HNMR: NMR spectra can confirm the development of a complex between active phytoconstituents and phospholipids. The chemical bonding is described by a significant change in signals arising in 1HNMR from atoms involved in complex formation. The creation of phytosomes is confirmed by wide signals from phytoconstituents and phospholipids, as well as a chemical shift matching to choline N-methyl.

^{13}CNMR: The shift in user specifies to the fatty acid chains may be understood in 13C NMR of phytochemical compounds and the stoichiometric intricate of phosphatidylcholine and herbaceous excerpt.

FTIR: FTIR spectra analysis of phytosomes complex in solid state after lyophilization compared to micro-dispersion in water at various intervals.

2.7.4 Transition temperature

The differential scanning calorimetry thermal analysis apparatus is used to measure the temperature variation of physical properties of a sample against time and this method is used to determine transition temperature.

2.7.5 Visualization of the morphology of phytosomes

The size and shape of phytosomes and their visual appearance are done by different microscopic techniques like scanning electron microscopy and transmission electron microscopy. Various factors affect and alter the size and shape of phytosomes like the shape and size of phytosomes can be affected by lipid purity grade.

2.7.6 Surface tension activity measurement

The surface tension is measured using the ring method Du Nouy ring tensiometer.

2.7.7 Crystallinity

Crystalline properties of the phytophospholipid complex can be predicted by X-ray diffraction analysis. The peak obtained in the X-ray diffraction pattern specifies the product properties.

2.7.8 Vesicle stability

Vesicle stability is determined by molecular size, polydispersity index (PDI), and zeta potential describing the vesicle stability. PDI value of phytosomes is determined and phytosomes with a PDI value of less than 0.5 are stable, while those with a zeta potential greater than 30 mV are considered stable complexes.

2.7.9 In vitro and in vivo evaluations

In vitro and *in vivo* evaluation depend on the properties of the drug, and their chief phytoconstituents bounded by phospholipid layer and on the basis of that particular animal model are selected for its evaluation.

2.8 Phytosomes studies

Moscarella et al. [13] developed silicide phytosome from the *Silybum marianum* plant, which was tested in rats for its antioxidant and free radical scavenging activities against liver oxidative damage caused by CC14 and paracetamol (high doses) [8–24]. Silipide protects hepatocytes from oxidative damage by inhibiting lipid peroxidation and scavenging reactive oxygen species, which may be the mechanism.

Yanyu et al. [14] studied the pharmacokinetics of silymarin phytosome was investigated in rats. Because of an outstanding improvement in the lipophilic characteristics of silybin phospholipid complex and improvement in the biological impact of silybin, the bioavailability of silybin in rats was significantly raised following oral administration of silybin phospholipid complex in the tests.

Maiti et al. [11] prepared curcumin (a flavonoid derived from the *Curcuma longa* plant, turmeric) and naringenin (a flavonoid derived from the grape fruit *Vitis vinifera*)

phytosomes were produced in two separate experiments. In all dosage levels examined, the complex's antioxidant efficacy outperformed pure curcumin. In a separate investigation, the created phytosome of naringenin had more antioxidant activity and a longer duration of action than the free compound, which might be attributable to a reduction in the molecule's quick removal from the body.

Panda et al. [12] demonstrated that *Ginkgo biloba* phytosomes (200 mg/kg) were shown to dramatically reduce isoproterenol-induced cardiac necrosis. The cardioprotective actions of phytosomes were further confirmed by histopathological study of the myocardium. Reduced myocardial necrosis (as demonstrated by lower AST, LDH, and CPK levels, as well as histoarchitectural alterations) and enhanced endogenous antioxidants all end up contributing to its cardioprotective impact.

Kidd et al. [10] prepared silybin and substitute silymarin flavonoids oligoynes from phyllanthus niruri, curcumin and pertaining diphenol curcuminoids, herbal tea flavan-3-ol catechins, and nigella sativa proanthocyanin combined (including catechin and epicatechin monomers and oligomers) with poor bioavailability and their complexation into phytosomes to overcome this drawback, and it was reported that conversion into phytosomes has improved for each of those preparations. In phytosome technology, individual polyphenol molecules and one or more molecules of the phospholipid phosphatidylcholine establish intermolecular connections (PC). Each polyphenol is coated by PC molecule(s) according to molecular imaging; following oral consumption, the amphipathic PC molecules "usher" the polyphenol past the intestinal epithelial cell outer membrane, eventually reaching the bloodstream. PC has been shown to have therapeutic efficacy and contributes to phytosome *in vivo* effects. Phytosome technology significantly increases the therapeutic applicability of polyphenols and other poorly absorbed plant medicines as molecular delivery vehicles.

Gupta and Dixit [17] have demonstrated that integrating a large quantity of curcumin in a topical formulation does not result in improved bioavailability. They produced a curcumin-phosphatidylcholine combination and analyzed it using TLC, DSC, Melting point, and FT-IR. They studied the effects of vesicular systems such as liposomes, niosomes, and phytovesicles. Therefore, they found that phytovesicles had better antioxidant and anti-aging capabilities than other colloidal carriers, which might be due to the complex's amphiphilic character, which greatly enhances the curcumin's water and lipid miscibility.

Cuomo et al. [18] considered that in a randomization, double-blind cross-over design on humans, researchers studied the relative absorption of a standardized curcuminoid combination and compared it to a lecithin formulation (Meriva). They found that the Meriva had higher absorption and a better plasma curcuminoid profile than an unformulated curcuminoid combination at a far lower dose.

Kuamwat et al. [15] considered that gallic acid and its derivatives contain polyphenolic chemical groups, however they are less lipophilic. To overcome this limitation, they created a combination of gallic acid and phospholipids in varying proportions to increase gallic acid's lipophilic characteristics. UV-visible spectroscopy (UV), infrared spectrometry (IR), and differential scanning calorimetric (DSC) techniques were used to investigate the complex's physicochemical characteristics, such as solubility and dissolution. The results indicated that gallic and phospholipids in gallic-phospholipids complex were connected by non-covalent bonds and did not produce another molecule. It was also discovered that the complex was an excellent DPPH radical scavenger and had significant antioxidant activity.

Sandhya et al. [16] have undertaken preclinical research on a new polyherbal phytocomplex hair growth advancement cream using aqueous extracts of

Trichosanthescucumerica and Abrusprecatoriuslinn. Extraction of both plants, chemical testing of both extracts, synthesis of phytophosphatidylcholine complex, formulation, and evaluation of cream comprising polyherbal phyto-complex were all part of the experimental experiment. Preclinical studies showed that the designed 2 percent polyherbal phytocomplex hair development advanced cream was an excellent hair growth booster, with results comparable to minoxidil 2 percent. The antigen phase saw a considerable increase in the number of hair follicles, indicating that the formulation may be utilized to treat alopecia. The comparative effects of ethanolic extracts of Wrightia arborea leaves and their phytosomes were investigated by Lakshmi et al. [19].

The phytosomes were able to cure the wound at a rate of 90.40 percent, but the ethanolic extract alone could only repair it at a rate of 65.63 percent.

Zhang et al. [24] revealed curcumin phytosome-infused chitosan microspheres (Cur-PS-CMs) were created by summarizing curcumin phytosomes (Cur-PSs) in chitosan microspheres utilizing ionotropic gelation, and the new Cur-PS-CMs system promoted oral absorption and extended curcumin retention time better than single Cur-PSs or Cur-CMs. As a result, PS-CMs might be used to deliver lipophilic medicines with poor water solubility and restricted oral bioavailability.

Das et al. [9] investigated Rutin (*Ruta graveolens*) is a complex carbohydrate that has antioxidant, anti-inflammatory, antithrombotic, antineoplastic, and antiplatelet activities. It is used to treat capillary fragility, hypertension, UV-induced cutaneous oxidative stress, hepatic and blood cholesterol, cataract, and cardiovascular disease. The Rutin phytosomes were seen to be more capable of penetrating the impenetrable stratum corneum than the Rutin in its free form. Rutin phytosomes were taken up by the skin at a rate of 33.133 percent, whereas Rutin was taken up by the skin at a rate of 13 0.87 percent.

Sabzichi et al. [23] have manufactured nanophytosomes containing luteolin to boost luteolin bioavailability and latent focusing in breast cancer cells, and found that co-treating cells with nanoparticles containing luteolin and doxorubicin resulted in the highest rate of cell death in MDA-MB 231 (Human Breast Carcinoma) cells {$p < 0.05$ (Statistical analysis was used by ANOVA and the significance level was considered as 95% $p < 0.05$)}. They hypothesized that luteolin-loaded nanoparticles lowered Nrf2 (Nuclear factor erythroid 2-related factor) gene expression at the mRNA level in cells more than luteolin alone ($p < 0.05$), and that expression of downstream Nrf2 genes such as Ho1 and MDR1 was also reduced ($p < 0.05$). The suppression of Nrf-2 expression resulted in a significant increase in cancer cell death ($p < 0.05$). They also suggested that phytosome invention might improve chemotherapy efficacy by overcoming cancer cell resistance and increasing cancer cell penetrability to substance operators and that it could be used as a delivery mechanism to improve cancer patient treatment protocols.

Yang et al. studied the comparison, "PEG-MMC-loaded phytosomes, FA-PEG-MMC-loaded phytosomes had superior cellular absorption in HeLa cells and better accumulation in H22 tumor-bearing animals. Furthermore, as compared to free MMC injection, FA-PEG-MMC-loaded phytosomes had higher cytotoxic activity *in vitro* and a better anticancer impact *in vivo*. FA-PEG-MMC-loaded phytosomes, they said, might be useful drug delivery methods for expanding the therapeutic window of MMC in clinical studies".

Shalini et al. [7] worked on a comparison of the antiproliferative activity was done with quercetin and its phytosomes and the MTT test (colorimetric assay) was used to assess the antiproliferative activity of a methanolic extract of Terminalia arjuna bark and its phytosomes on the human breast cancer cell line MCF-7, and its activities were compared to quercetin and its phytosomes. IC_{50} (concentration of compound required to inhibit 50% cell growth) of *Terminalia arjuna* bark methanolic extract and *Terminalia arjuna* bark

Extract Phytosome against cancer cell lines was found to be 25 and 15 μg/ml respectively, whereas that of quercetin and its phytosomes were found to be 2 and 0.7 μg/ml, respectively. The findings imply that quercetin phytosomes and *Terminalia arjuna* bark extract phytosomes are pharmacologically active and exert greater antiproliferative effects on MCF-7 cells than pure methanolic plant extract and pure quercetin, respectively.

Elnaggar et al. [21] have formulated tween-modified monoolein cubosomes (T-cubs) that were loaded with piperine (PIP) and tested with several bioactive surfactants (Tween 80, poloxamer, and Cremophor) to see if Cubs might enable PIP *in vitro* release. The ability of uncovered T-cubs to substantially improve PIP intellectual impact and reinstate psychological function to a normal level is investigated *in vivo*. Tween's brain-targeting impact was suggested by the predominance of T-cubs over others. Toxicological studies investigated the health of cubs' kidneys, livers, and even their brains. T-cubs showed anti-inflammatory and anti-apoptotic activity in response to loaded PIP, indicating that they can halt AD progression. Novel oral nanoparticles have been proposed that exhibit potential *in vitro* and *in vivo* properties, as well as a high level of wellbeing, for the successful chronic treatment of Alzheimer's disease.

Mazumder et al. [8] studied the tissue repair efficacy of Sinigrinon HaCaT cells, one of the primary glucosinolates found in Brassicaceae plants, and was evaluated both alone and as a phytosome complex. The wound heals completely (100%) when the sinigrin-phytosome complex is used; however, the phytoconstituent alone only heals 71% of the time. Furthermore, sinigrin phytosomes have been shown to have increased anticancer action in A-375 melanoma cells.

2.9 Difference between phytosomes and liposomes

Both phytosomes and liposomes are novel approaches to increase the absorption and bioavailability of herbal extracts; however, they differ from each other as explained in **Table 1** and shown in **Figure 2**.

Sr. No.	Phytosomes	Liposomes
1	It is prepared by the interaction between the polar or hydrophilic part (head) of phospholipids and water-soluble plant extract and form a complex by chemical (hydrogen) bonds.	It is prepared by mixing phospholipids in a water-soluble substance, but here no chemical bonds are formed.
2	Phospholipids and substrate complexes are formed in stoichiometric ratio, depending on the plant extract used.	Thousands of phospholipid molecules are surrounded by the substance.
3	Phytosomes can increase in absorption of phytoconstituents and enhances the bioavailability of a substance	It can increase in absorption of phytoconstituents and bioavailability of substance is to a lesser extent than phytosomes
4	It has greater stability than liposomes due to phytophospholipid complexes are formed in phytosomes.	It has less stability than phytosomes has there is the absence of chemical bonding no complex is formed.
5	Solvents used in phytosomes preparation are having reduced the dielectric constant.	In liposomes buffer solution or water is used as solvent.

Table 1.
Difference between phytosomes and liposomes.

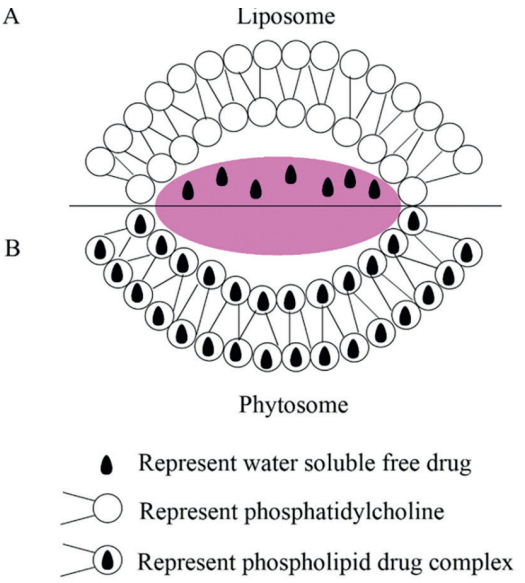

Figure 2.
Comparison between liposome and phytosome.

2.10 Marketed products

Various product available in market (**Table 2**) [12, 25–31, 33–35].

No.	Phytosomal Product	Phytoconstituent	Natural Source	Pharmacological activity	References
1	Hawthron Phytosomes	Hyperin, Quercitin	*Crateegus, Oxyacanthoids*	Antihypertension, Cardioprotective	[25]
2	Ginseng Phytosomes	Ginsenosides	*Panax Ginseng*	Immunomodulator, Nutraceutical	[26]
3	Curcumin Phytosome	Curcumin	*Curcuma Longa*	Osteoarthritis, Anti-Inflammatory, Anticancer	[27]
4	Escin B-Sitosterol Phytosome	Saponins	*Aesculus Hippocastanum* (Horse Chestnut Fruit)	Anti-Oedema	[28]
5	Green Tea Phytosome	Epigallocatechin, Catechin, Epicatechin-3-O-Gallate, Epigallocatechin-3-O-Gallate	*Camellia Sinesis* (Tea)	Nutraceutical, Systemic Antioxidant, Anticancer, Hepatoprotective, Anti-Inflammatory	[29]
6	OleaselectTM Phytosome	Polyphenol	*Olea europaea*	Anti-inflammatory, antihyperlipidemic	[30]
7	Glycyrrhetinic acid PhytosomeTM	Glycyrrhetinic acid	*Glycyrrhiza glabra* (Mulethi)	Anti-inflammatory, dermatitis	[31]

No.	Phytosomal Product	Phytoconstituent	Natural Source	Pharmacological activity	References
8	Silybin Phytosome [32]	Silybin, Silycristin, Isosilbin, Silydianin	*Silybium maranium* (Milk Thistle)	Hepatoprotective, Antioxidant for skin and liver	[33]
9	Mirtoselect Phytosome	Anthocyanosides	*Vaccinum myrtillus* (Bilberry)	Antioxidant, Improvement of Capillary Tone.	[34]
10	Ginkgo phytosomes	24% Ginkgo flavon glycosides	*Ginkgo biloba*	Protect the brain and vascular lining, antiageing agent	[12]
11	Visnadex Phytosome	Indena	*Amni visnaga*	Improve microcirculation	[35]

Table 2.
Marketed products.

3. Conclusion

Phytosome-loaded drug delivery systems are unique for the bioactive compounds having low solubility and bioavailability. Formation of complexes of plant-derived chemical with suitable excipients is one of the best ways to explore the best bioavailability and acceptance.

It is one of the lipid-based vesicular delivery systems that can be utilized to deliver pharmaceuticals and plant-derived nutraceuticals such polyphenolic chemicals in the phytosome. The phytosome, a newly developed food-grade delivery method, has the potential to lessen issues with the solubility and bioavailability of polyphenolic chemicals, making it useful in the creation of new medication and food compositions. Pharmaceutical firms might profit from using this delivery system to encapsulate enough potent phyto-ingredients to create new supplements. Additionally, phytosomes can increase the absorption of polyphenolic substances through the digestive system while reducing the amount required for delivery.

Furthermore, the preparation procedure of phytosomes is easy to fabricate and can be scaled up commercially. Being a potent candidate for bringing herbal-originated polyphenolic compounds into the efficient treatments of cancer and other diseases makes the phytosome technology a great encapsulation platform to be used in the nanoformulation of nutraceuticals in future.

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