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Phytosome as a Novel Carrier for Delivery of Phytochemicals: A Comprehensive Review

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ABSTRACT

Phytomedicine is known for its excellent therapeutic applications owing to phytoconstituents present in plants, with no or least side effects. But its low bioavailability due large molecular size, poor lipid solubility and lack of stability of bioactive compounds make hindrance in its efficacy. Different strategies have been developed to generate the effective carrier systems to enhance bioavailability of phytochemicals. One of the latest and most popular lipid-based carriers for delivering plants based pharmaceuticals and nutraceuticals is the phytosome. Phytosome is an emerging lipid based drug delivery approach which involves encapsulation of bioactive ingredient into phospholipid molecule mainly phosphatidylcholine. Phytosomes as phyto-phospholipid complexes lead to target drug delivery, better bioavailability and stability, enhanced pharmacological efficacy as well as the protection of bioactive compounds from chemical and physical degradation. Due to easy preparation of the bilayer vesicles and their effectiveness, phytosomes have been extensively employed and approved by the scientific literature. In this review, a phytosome technology, its structural components, formulation techniques, optimization, characterization approaches as well as merits and demerits are comprehensively discussed. Moreover, phytosome based market products and recent research is presented. It is concluded that phytosome technology is a gift for herbal extracts and phytochemicals that are inadequately bioavailable and have well-established processing methodologies as well as verified analytical techniques.

Keywords: Phytomedicine; Novel drug delivery system; Phytosome; Liposome; Bioavailability; Phytochemicals; Phosphatidylcholine; Thin layer hydration technique; Biodegradable; Supercritical anti-solvent precipitation.

Objectives

(i) To reveal the importance of plant based medicine and development era of novel drug delivery systems.

(ii) To elucidate the concept of phytosome technology designated for better bioavailability and target delivery of phytochemicals.

(iii) To highlight systematically the structural components, fabrication methods, optimization, and characterization techniques of phytosomes.

(iv) To enlist the merits and demerits of phytosomes.

(v) To review the importance of phytosomes through studying phytosome based market products and recent advanced research.

1. Introduction

Phytotherapy based on the medicinal herbs is an important part of healthcare system, owing to its better safety profile, high efficacy, low cost, easy availability and least or no side effects (Jahangir et al., 2020; Mishra et al., 2022). Phytomedicines have always been highly beneficial to mankind for treating implacable diseases from time immemorial and are utilized extensively by the globe (Naik et al., 2020; Singh et al., 2020). In the recent years, phytomedicines have recently attracted the attention of people and researchers all over the world due to their prominent therapeutic benefits and better patient's compliance (Dongare et al., 2021). Plant-derived bioactive

compounds including phenolic compounds, lignans, alkaloids, etc. possess a plethora of medicinal properties advantageous for humans such as antimicrobial, anti-allergic, antioxidant, anticancer, anti-diabetic anti-inflammatory activities (Tran et al., 2020). But, the traditional dose forms for herbal medication have certain limitation including inadequate absorption, lower penetration across biological membrane and reduced bioavailability due to large molecular size as well as lipophilicity, which decrease their applications (Singh et al., 2020).

Conventional dosage forms are also unable to control the rate of the drug delivery to the target site. The distribution of medicine in non-target site may necessitates a therapeutic drug dose which could significantly exceed the quantity required in the target site and the higher dose of drug often cause serious adverse effects during the treatment (Singh et al., 2021).

The effectiveness of plant based medicines can be enhanced by their incorporation into some proper dosage forms in a systematic manner (Dongare et al., 2021). So, it is necessary to do a research on nano-carrier based drug delivery as an alternative approach to eliminate problems of conventional dose and low bioavailability for better efficacy, effective drug targeting and patient compliance (Shirsath and Goswami, 2019).

2. Novel drug delivery systems (NDDSs)

Drug delivery systems are defined devices which transport the therapeutic agents to a specific target site inside body (Sivadasan et al., 2023). Development of the novel drug delivery systems (NDDSs) is a new emerging approach for herbal extracts and bioactive compounds (Singh et al., 2014). During the past few decades, remarkable advancements have been made to develop of the novel systems of drug delivery which involves encapsulation of phytoconstituents (Rahman et al., 2020). Novel drug delivery system decreases limitations of conventional drug delivery systems. This approach helps to increase the solubility, bioavailability, and stability of herbal drugs and phytoconstituents (Kattyar et al., 2022).

An ideally designed drug delivery system ensures the delivery of a certain amount of drug to a specific target site at a proper rate and time as desired by the physiological needs of body. Thus, novel drug delivery systems are the carriers which control the drug dosage in a medically appropriate range, for a longer duration and carry drug content to specific target site as desired according to requirement (Singh et al., 2021). Controlled release of drug is pre-designed to ensure an effective drug content at the target site, thus reducing toxic side effects and promoting the therapeutic benefits (Sivadasan et al., 2023).

Different techniques have been developed to produce effective novel nano-carriers in order to increment the bioavailability of phytoconstituents (Barani et al., 2021). Mostly vesicular drug delivery systems are employed as nanocarriers for phytoconstituents, in which active phytochemicals are enclosed in a sphere-shaped complex (Supraja and Mulangi, 2019). Various vesicular drug delivery systems such phytosomes, transferosomes, ethosomes, liposomes, colloidosomes etc. have been developed in order to carry the drug to target site without its metabolism or degradation (Chivte et al., 2017).

Table 1. Vesicular novel drug delivery systems (Barani et al., 2021; Abdul R. et al., 2022; Sivadasan et al., 2023)

Novel drug delivery system	Development	Composition	Administration
Liposomes	Discovered in 1961 by a British scientist Dr. Alec Bangham	Phospholipid and cholesterol	Parenteral topical, oral and transdermal
Niosomes	L'Oreal generated and patented first niosome formulation in 1975	Nonionic surfactant and cholesterol	Oral, transdermal, and parenteral topical
Cubosomes	1980	Amphiphilic lipids in the presence of a suitable stabilizer	Oral, transdermal, ocular and chemotherapeutic administration
Phytosomes	An Italian pharmaceutical company, Indena developed phytosomes in 1989.	Phospholipid and polyphenolic phytoconstituents	Oral, transdermal, and parenteral topical
Transfersomes	Transfersomes were developed in 1990s by Idea, Munich, Germany.	Phospholipid and surfactant	Topical and transdermal
Ethosomes	1996	Phospholipid, polyglycol, alcohol, and water	Topical and transdermal

3. Phytosome technology

Phytosomes also known as herbosomes are an advanced novel form of phyto-constituent which are better absorbed topically, orally and transdermally (Gaurav et al., 2021). Phytosome is a phospholipid complexation patented technology which was invented in 1989 by Indena, an Italian nutraceutical and pharmaceutical company (Lu et al., 2019). The term "phytosome" is made up of two words, "phyto" meaning plant and "some" meaning cell-like (Kattyar et al., 2022). *'Phyto'* implies bioactive portion of phytosomal complex originated from plant and '*some'* indicates that the structure of complex is similar to the cell (Ghanbarzadeh et al., 2016). The phytosomes are vesicular complexes in which phospholipids mainly phosphatidylcholine (PC) are bonded to phytoconstituents though hydrogen bonding (Gaurav et al., 2021). In phytosomal complex, standardized extract of

plant or hydrophilic phytoconstituents are incorporated into phospholipid molecules to form a lipid compatible vesicular complex (Singh et al., 2014).

As a novel formulation, phytosomes exhibit excellent benefits as compared to the conventional formulations of herbal extracts and bioactive components. Phytosome technology mainly increases the bioavailability, lipid solubility and gastrointestinal solubility of the bioactive compounds. For example, Vasicine is utilized for the treatment of bronchitis and asthma and is a potential bronchodilator. Due to low solubility, its absorption in GIT is decreased leading to low bioavailability of vasicine. By employing the phytosome technology, its solubility and absorption were increased which leaded to better bioavailability of vasicine (Kattyar et al., 2022). Other benefits include incremented ability to cross cell membranes, stability, sustained delivery, and prevention from toxicity and chemical or physical degradation (Singh et al., 2014). Research have proven the higher efficacy of the phytosomes, in aspects of both reduced dosage and pharmacological potential (Barani et al., 2021). Phytosomes exhibit better transdermal drug distribution and have an extensive scope in cosmeticology (Gaurav et al., 2021).

Phytosomes of various plants such as *Hedyotis corymbosa* (Kumar et al., 2023), *Nicotiana tabacum* var. Virginia (Chittasupho et al., 2023), *Moringa oleifera* (Wanjiru et al., 2022), *Punica granatum* L. (Kazemi et al., 2022), *Geophila repens* (Rajamma et al., 2022), *Vaccinium macrocarpon* (Bresciani et al., 2021), *Intsia bijuga* (Sari et al., 2021), Aloe vera (Murugesan et al., 2021), *Trigonella foenum-graecum (Sharma et al., 2020), Centella asiatica* L. (Sbrini et al., 2020), *Ginkgo biloba* (Carignani et al., 2020), *Bombax ceiba* (Karole and Gupta, 2019), *Diospyros kaki* L. (Direito et al., 2019), *Annona muricata* L. (Mancini et al., 2018), Cinnamon (Nazari et al., 2019), *Terminalia Arjuna* (Shende et al., 2018), *Vitis vinifera* L. (Surini et al., 2018), *Abutilon indicum* and *Piper longum (Sharma and Sahu, 2016), Aegle marmelos* (Dhase and Saboo, 2015) have been reported with enhanced bioavailability and pharmacological properties. In nutshell, phyto-phospholipid technology act as a boon for the badly absorbed phytochemicals and herbal extract (Anjana et al., 2017).

4. Structure of phytosomes

Phytosomes have chemical structures similar to cell membranes (Ghanbarzadeh et al., 2016). They are produced by the interactions between polar head of phospholipid molecules and active phytoconstituents (Khan et al., 2013). These interactions between phytoconstituents and the phospholipids make phyto-phospholipid complexes in which polar head of phospholipids is embedded but two long chains of fatty acid do not involve in phytosomal complex formulation. The fatty acid chains are able to migrate and enclose the polar portion of the phytosomes to make a lipid soluble surface (Ghanbarzadeh et al., 2016).

5. Phytosomes differ from liposomes

On dilution in water, phytosomal complexes form agglomerates similar to cells which indicates resemblance to liposomes. It is important to distinguish phytosomes from liposomes in order to appreciate their uniqueness (Table 2). The key structural difference between them is that the bioactive compound of phytosomes is a part of the membrane itself, whereas active ingredient of liposomes is located between layers of the membranes or within the water soluble cavity. A phytosomal unit is a molecular level association which involves as few as two molecules, one phospholipid and one polyphenol molecule bonded by hydrogen bonding. Thus, a link is formed between

bioactive phytochemicals and polar portion of the phospholipids, being an integrated constituent of the cell membrane.

The unit liposome is an association which involves the aggregate of the hundreds of phospholipids into a spherule, in which other bioactive molecules are compartmentalized but not particularly bonded. The phytosomes show a better stability, absorption and bioavailability than liposomes owing to the formation of stable hydrogen bonds. For phytosome, optimum molar ratios of phytoactive compound to phospholipid are 1:1 or 1:2. While in liposomes, the molar ratio of phospholipid molecules are usually ten times more than phytoactive compound. The liposome concept is unproven as an effective oral delivery vehicle, whereas the phytosomes are known to significantly enhance the oral delivery (Kidd, 2009; Ghanbarzadeh et al., 2016; Lu et al., 2019).

Table 2. Difference between phytosome and liposome

Property	**Phytosome**	**Liposome**
Structure	Bioactive compound is a part of the membrane itself	Active ingredient is located between layers of the membranes or within the water soluble cavity
Nature of bond	Hydrogen bonding	No chemical bonding
Phospholipid: Bioactive components	1:1 or 1:2	Phospholipid molecules are usually ten times more than bioactive compound
Stability	High	Lower than phytosome
Bioavailability	High	Lower than phytosome

6. Components of Phyto-phospholipid complex

6.1. Bioactive phytoconstituents

The bioactive compounds of plant extracts recognized by researchers are usually defined on the basis of stronger *in vitro* biological activities as compared to their *in vivo* activities. These bioactive substances are polyphenols mostly (Lu et al., 2019). Some of the bioactive polyphenolic compounds of herbs are hydrophilic and cannot cross biological cell membranes. While, others show high lipid soluble properties and are unable to be dissolved in the aqueous gastro-intestinal fluid, including rutin and curcumin. Phytosomes do not only enhance solubility of the lipid soluble compounds in polar phase but also improve membrane penetrability of the water-soluble agents. Moreover, the formation of phytosomes can prevent polyphenolic compounds from degradation by external conditions, including hydrolysis, oxidation, and photolysis (Kidd, 2009).

Besides polyphenols, many other biologically active compounds from plant extracts can also be encapsulated with phospholipids (Lu et al., 2019) such as piperine (Islam et al., 2022), allicin (Nining et al., 2021) and evodiamine (Tan et al., 2012). Therefore, phytosome technology is appropriate for any bioactive substance and not limited to only polyphenols (Kidd, 2009).

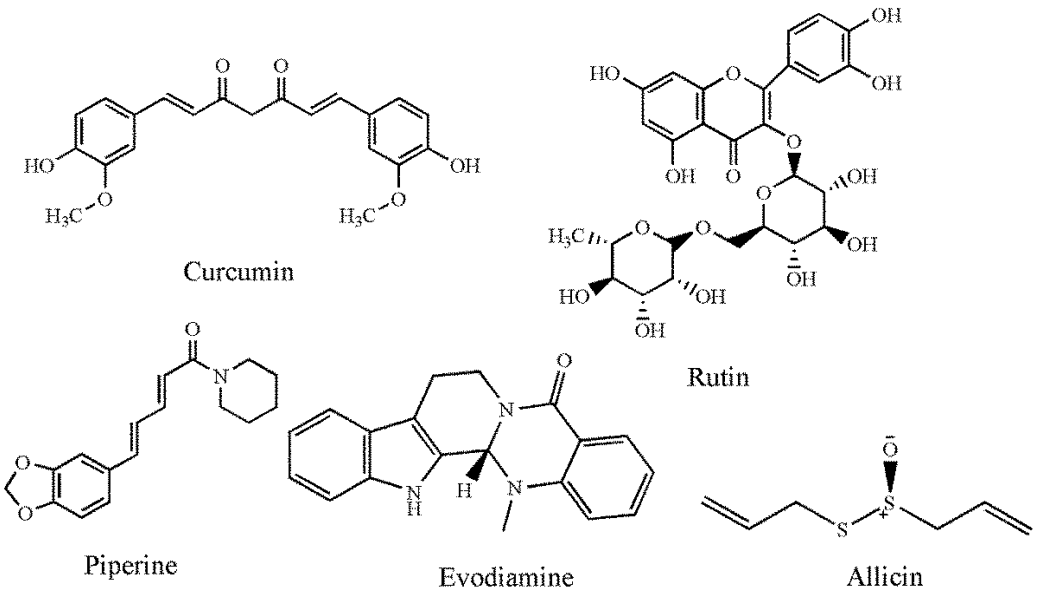

Figure 1. Structure of bioactive phytoconstituents

6.2. Phospholipids

Phospholipids have outstanding properties of an amphiphilicity and excellent biocompatibility. These remarkable characteristics make phospholipids the most appropriate to be utilized as an important pharmaceutical agent and they have a number of applications in the drug delivery systems. Phospholipids are basically lipids consisting of a polar part, phosphorus and non-polar component in their molecular structures. Phospholipids are compounds in which hydrophilic portion and the hydrophobic acyl chains are bonded to the alcohol group. There exist a huge variety of phospholipids due to variations in polar head portion, alcohols and aliphatic chains. Phospholipids can be classified depending on the backbone into two classes, glycerophospholipids and sphingomyelins. Glycerophospholipids include phosphatidylglycerol (PG), phosphatidylinositol (PI), phosphatidic acid (PA), phosphatidylserine (PS), phosphatidylethanolamine (PE), and phosphatidylcholine (PC). PC, PS, and PE are the main phospholipids utilized to formulate phytosomal complexes which are made up of two chains of non-polar hydrocarbon and a polar portion (Li et al., 2015).

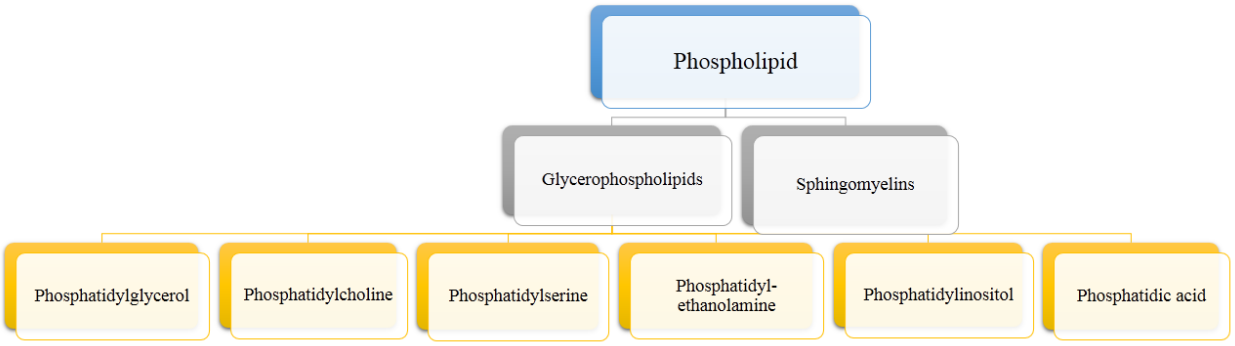

Figure 2. Classification of phospholipids (Li et al., 2015)

Phosphatidylcholine is mostly employed to formulate phytosomes among all of these phospholipids (Lu et al., 2019). Phosphatidylcholine is a bi-functional molecule, in which choline portion is hydrophilic and the

phosphatidyl portion is lipophilic (Agrawal et al., 2012). Its benefits are its amphilic characteristics that make it moderately soluble in aqueous media and the lipid media. Furthermore, it is an important part of biological membranes, highly biocompatible and it is shows low toxicity. It shows liver protective effects and exhibit clinical activities in treating liver disorders including fatty liver and hepatitis (Lu et al., 2019).

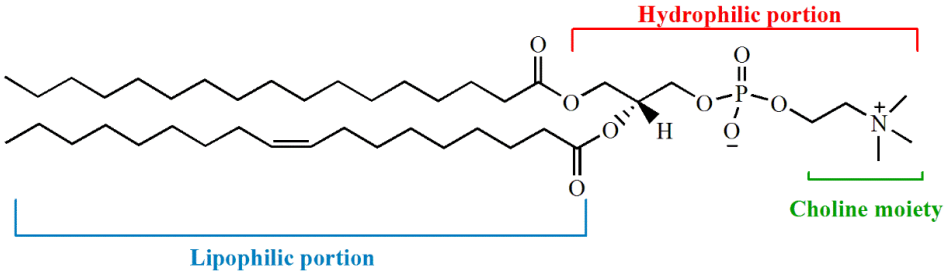

Figure 3. Structure of Phosphatidylcholine

6.3. Solvent system

Various solvents have been reported as a medium of reaction to fabricate phytosome (Khan et al., 2013). Mostly, polar aprotic solvents are used in preparation of phytosome to serve as an appropriate environment to support hydrogen bond formation (Telange et al., 2017; Vu et al., 2018). In aprotic solvents, no hydrogen atom is directly in connection with an electronegative atom and possess no ability of hydrogen bonding. Conventionally, such solvents, including methylene chloride, aromatic hydrocarbons, cyclic ethers, and *ethyl ethanoate* have been used for the formation of phytosomes (Khan et al., 2013). However, such solvents have been replaced by protic solvents such as methanol and ethanol (Lu et al., 2019).

In protic solvents like ethanol and methanol, at least one hydrogen atom is directly connected to an electronegative atom (Patel et al., 2009). The hydrogen bonds formation between active compounds and phospholipid molecules offers various benefits, including better stability profile, high entrapment efficiency and enhanced permeability through cell membranes, therefore leading to greater bioavailability and enhanced efficacy (Permana et al., 2020). The hydrogen bonding has been reported in methanol (Hammam et al., 2017). However, ethanol is considered as an effective solvent owing to the high yield of phytosomes and lower amount of residues (Patel et al., 2009). Ethanol is widely chosen as solvent in various studies including fabrication of *Nicotiana tabacum* var. Virginia leaf extract phytosomes (Chittasupho et al., 2023), naringenin loaded dipalmitoylphosphatidylcholine phytosomes (Yu et al., 2020) and berberine-phospholipid complex-based phytosomes (Yu et al., 2016).

Despite the fact that most of fabrication techniques involve only one solvent, mixed solvents have also been reported. In mixed solvent system, the phospholipid molecules and extract are dissolved in a two different solvent have been reported in various studies. Methanol and dichloromethane, diethyl ether and water, and ethanol and dichloromethane are some examples of the mixed solvent systems (Barani et al., 2021). Some liposomal complexes of drugs work in presence of water or buffer as the dielectric constant of phytosomal complexes show weak interaction with solvent (Patel et al., 2009).

Lately, various studies used the supercritical fluid (SCF) based approaches in order to control the shape, size, and other morphological features of produce micronic and submicronic particles. One of the SCF based methods,

is supercritical anti-solvent technology, in which a supercritical fluid, usually CO_2, is employed as an anti-solvent to decrease the solubility of solute in the solvent. This technique is notably a promising technique to produce particles with controlled size distribution (Semalty, 2014). Supercritical anti-solvent precipitation technique was utilized to form puerarin loaded phospholipid complexes (Li et al., 2008).

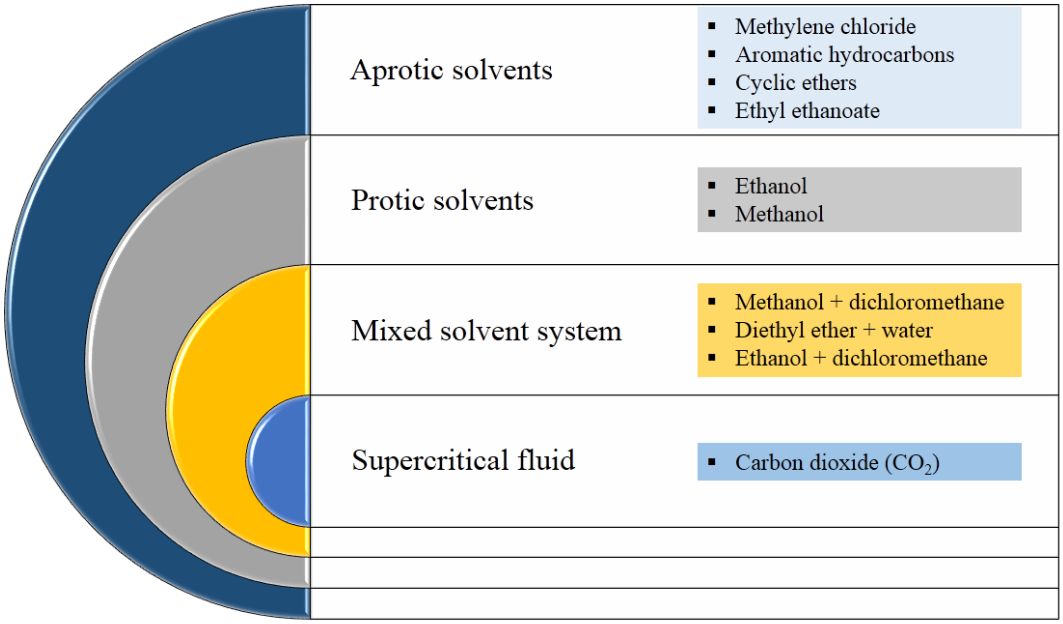

Figure 4. Solvent systems for phytosome formulation (Khan *et al.*, 2013; Semalty, 2014; Lu *et al.*, 2019; Barani *et al.*, 2021)

6.4. Stoichiometric ratio of phytoconstituents and phospholipids

Generally, phytosomes are formed by reaction of a natural or synthetic phospholipid molecule with the bioactive compounds in a molar ratio of 0.5-2.0 (Tripathy et al., 2013). While, stoichiometrically, a ratio of 1:1 is thought as the most effective ratio for the formulation of phytosomal complexes (Chauhan et al., 2009). For instance, quercetin loaded phytosomal complexes fabrication by mixing quercetin and lipoid in a ratio (molar) of 1:1 has been reported (Zhang et al., 2016). However, various stoichiometric ratios of phytosomal components have been reported. Silymarin phytosomes were prepared using various ratios of 1:5, 1:10, and 1:15 and it was observed that the phytosomal complexes prepared with a ratio of 1:5 exhibited the highest loading capacity and the best physical properties (Maryana et al., 2016). Hence, a stoichiometric ratio of 1:1 is not optimum in all cases for preparation of phytosomes. For various kind of drugs, the ratio of phytoconstituents and phospholipid are experimentally adjusted with respect to a distinct factor.

7. Methods of formulation of phytosomes

Phytosomes are fabricated by treatment of plant extract into phospholipids mostly phosphatidylcholine (Kattyar et al., 2022). Several techniques have been proposed for the formulation of phytosome which include solvent evaporation method, thin layer hydration technique, anti-solvent precipitation technique, co-solvent lyophilization method (Anjana et al., 2017), and salting-out technique (Barani et al., 2021).

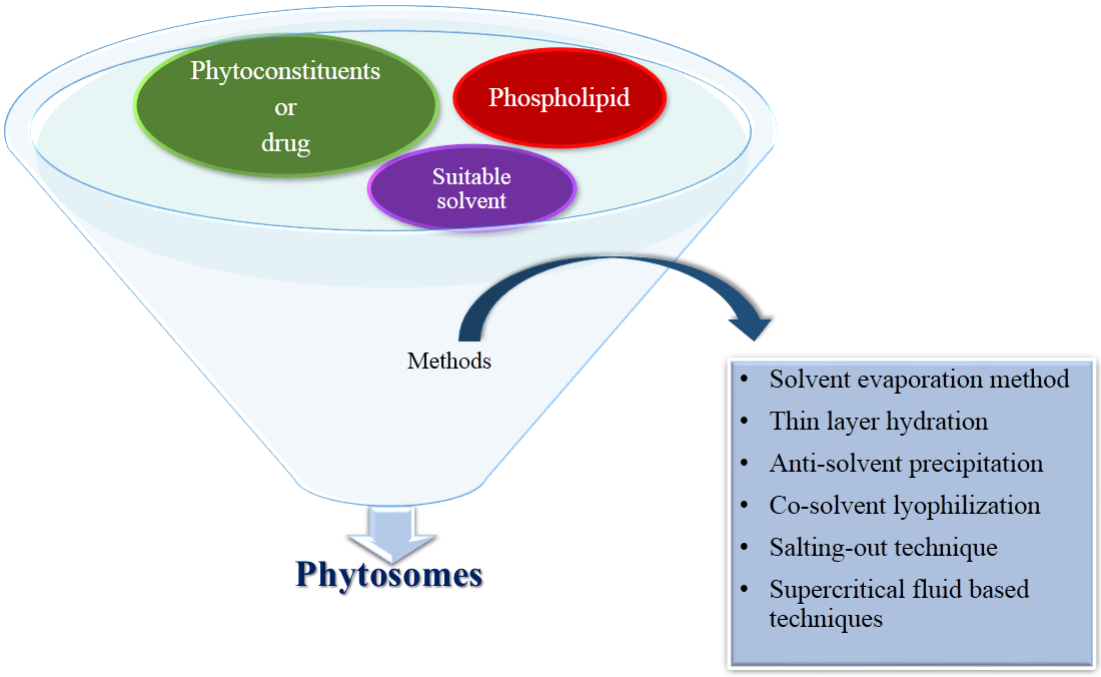

Figure 5. Fabrication of phytosomes (Anjana et al., 2017; Barani et al., 2021)

7.1. Solvent evaporation method

Solvent evaporation is a conventional and commonly employed approach for the fabrication of phytosomes. Briefly, active phytoconstituents and phosphatidylcholine in a designed stoichiometric ratio are placed in a flask and dispersed in a suitable solvent by the process of heating at an optimum constant temperature for a specific duration. Solvent is evaporated under vacuum to obtain fabricated phytosomes (Lu et al., 2019).The solvent evaporation method was applied to form evodiamine-phospholipid complexes (Liu, 2012). Berberine phytosomes were fabricated by using a solvent evaporation technique which was followed by some self-aggregation method in order to develop an effective delivery system of berberine (Yu et al., 2016). Phytosomes loading methanolic leaves extract of Aegle marmelos (bael) was also fabricated by solvent evaporation method (Dhase and Saboo, 2015).

7.2. Anti-solvent precipitation

In anti-solvent precipitation method, phospholipid and drug are refluxed in a favorable solvent. After concentrating the mixture formed, another solvent is added with continuous stirring for precipitation. Then, formed precipitates are filtered, collected and then kept in desiccators overnight (Anjana et al., 2017). *Allium cepa* phospholipid complexes (Habbu et al., 2015), Scorpion venom-standardized quercetin loaded phytosomal complexes (Alhakamy et al., 2022), icariin phytosomes (Alhakamy et al., 2020) were fabricated by anti-solvent precipitation.

7.3. Co-solvent lyophilization approach

In co-solvent lyophilization approach of phytosomes preparation, both phospholipid and drug are refluxed in an appropriate solvent separately. Both are then mixed by gentle stirring until a clear solution is formed. Then the resulted homogeneous mixture is freeze-dried and kept in an air tight bottle for its further utilization (Anjana et al., 2017). Kaempferol loaded phytosomes were fabricated by using lyophilization method (Telange et al., 2016).

7.4. Thin layer hydration method

In thin layer hydration method, phytochemicals and phospholipid are mixed in methanol and cholesterol is mixed in the dichloromethane. Then, evaporation of mixture is conducted using a rotary evaporator until the production of dry thin film. Generally, nitrogen gas is moved over thin film formed to get rid of organic solvents completely. Next, organic solvents are completely evaporated by vacuum drying. Then the film is hydrated using distilled water (Anjana et al., 2017). Formulation of *Vitis vinifera* L. seed extract phytosome by thin layer hydration method has been reported (Surini et al., 2018).

7.5. Salting out method

Diosmin phytosomes were prepared by salting out method. Following the salting out technique, diosmin and soy phosphatidylcholine phospholipid were mixed in a mixture of dehydrated ethanol, dimethyl sulfoxide, and chloroform in ratio of 2:2:3 to make a volume of 35 ml. Then the mixture was agitated employing a magnetic stirrer overnight and 75 ml of n-hexane was added into solution until precipitates formation (Freag et al., 2013). Piperine phytosomes was fabricated by salting out method (Islam et al., 2022).

7.6. Supercritical fluid based techniques

Supercritical fluid is an effective tool for the fabrication of particles whose size ranges from 5 to 2000 nm. Different methods based on supercritical fluid, such as gas anti-solvent technique, rapid expansion of supercritical solutions, supercritical anti-solvent method, compressed anti-solvent approach and solution enhanced dispersion by supercritical fluids, have been employed to improve solubility of poorly soluble drug ingredients (Karataş and Turhan, 2015). Supercritical anti-solvent precipitation technique was proposed to form puerarin loaded phospholipid complexes and it was found that the supercritical fluid method was better than the conventional approaches for preparation of drug loaded phytosomes (Li *et al.*, 2008).

7.7. Optimization

Phytosomes are optimized utilizing a Box–Behnken experimental design or any other suitable design. In a study of Icariin phytosomes, an experimental design containing three parameter was employed for preparation of phytosomes. Molar ratio of icariin to phospholipid, temperature and refluxing time were the independent parameters, while response was vesicle size. Design-Expert software was employed to obtain 15 experiments. Appropriate precision ratio as well as adjusted and predicted coefficients of determination were calculated and used to select the appropriate model for a response. The equation for the best fitting model was also obtained. ANOVA was implemented to statistically assess the measured response to determine significance of parameters at $p \leq 0.05$. Three dimensional and interaction plots were formed to observe interaction between the studied parameters (Alhakamy et al., 2020).

8. Characterization

8.1. Solubility and partition coefficient

Determination of the n-octanol/water partition coefficient (P) and solubility in either water or organic solvents is necessary to characterize bioactive components, phytosomes and physical mixtures. Generally, phytosomal

complexes have better hydrophilicity and lipophilicity than bioactive components (Ghanbarzadeh et al., 2016). An investigation confirmed that embelin phytosomes have greater solubility in water and n-octanol than crude embelin and physical mixtures (Pathan and Bhandari, 2011). In another study, a significant increase was observed in the hydrophilicity and lipophilicity of the silymarin phytosomal complex as compared to pure silymarin (Shriram et al., 2022).

8.2. Vesicle size, polydispersity index and zeta potential

Vesicles size, polydispersity index (PDI) and zeta potential are very important characteristics of phytosomes which are associated to their stability and reliability. Phytosomes with high zeta potential have great electrostatic repulsion between the particles that indicates the higher stability. The average size of phospholipid complexes generally ranges from 50 nm to 100 µm. The particle size and polydispersity index and zeta potential are measured utilizing dynamic light scattering with a particle size analyzer. In a study, *Moringa oleifera* phytosomal formulation exhibited 296 ± 0.29 nm particle size, polydispersity index of 0.106 ± 0.002 and zeta potential of −40.1 ± 1.19 mV (Wanjiru et al., 2022).

8.3. Visualization

Scanning electron microscopy (SEM), transmission electron microscopy (TEM), and atomic force microscopy (AFM) can be used to study the morphology of phytosomes. Investigation of surface morphology of phytosomes is usually a crucial approach to detect the mechanisms of entrapment as well as any probable impurities present on the surface (Semalty et al., 2010). SEM yield important insights into the surface morphology and solid state properties of phytosomal complexes. SEM revealed that bioactive compounds can be visualized in a highly crystalline form, which disappeared after complex formation. TEM is employed to study the crystallization and dispersion of nano-particles and to estimate the particle size. TEM showed that phyto-phospholipid complexes exhibit vesicle-like structures after dilution in distilled water under slight shaking (Ghanbarzadeh et al., 2016). SEM and TEM visualization of Naringenin loaded phytosomes indicated spherical shape and uniform structure (Metkari et al., 2023).

AFM reveal the morphological features and vesicle size of phytosomal formulations. AFM analysis of diosgenin phytosomes indicated spherical morphology of phytosomes. The vesicle size determined by AFM was greater than the vesicle size estimated by dynamic light scattering. The larger size might be due to the merging of phytosomal vesicles during process of drying (Xu et al., 2019). AFM micrographs of mitomycin C-soybean phosphatidylcholine loaded phytosomes and *Cassia auriculata* phytosome showed spherical and intact vesicles (Hou et al., 2013; Rahman, 2021). In general, the phytosomes surface characterizations do not show any crystalline structures or any impurities. The morphological studies have confirmed that the phytosomal structures have a spherical shape (Semalty et al., 2012).

8.4. Entrapment efficiency

Entrapment efficiency of phytosomes can be estimated by utilizing ultra-centrifugation (Wanjiru et al., 2022). For this purpose, sample is ultra-centrifuged at higher rpm-shorter durations or lower rpm-longer durations. Moreover, the supernatant is estimated in order to detect the free phytoconstituents or drug either by UV-Visible spectroscopy

or more precisely with high performance liquid chromatography (HPLC) (Ghanbarzadeh et al., 2016). Phytosome loading silymarin exhibited the drug entrapment efficiency of 97.169 ± 2.412 % (Maryana et al., 2016). Entrapment efficiency is calculated by the equation below:

$$\text{Entrapment Efficiency (\%)} = \frac{\text{Total extract loaded - Free extract in supernatant}}{\text{Total extract loaded}} \times 100$$

8.5. Structural confirmation of phyto-phospholipid complexes

Formation of phytosomal complex can be confirmed by its structural study through various techniques such as Ultraviolet-visible spectroscopy, Fourier transform infrared (FTIR) spectroscopy, Differential scanning calorimetry (DSC), X-ray diffraction (XRD) and Nuclear magnetic resonance (NMR) spectroscopy (Lu et al., 2019).

8.5.1. Ultraviolet-Visible spectroscopy

Specimens that are able to reflect in Ultraviolet and visible light can be utilized to determine their structural characteristics. Most of investigations showed no specific difference in UV light absorption properties of components before and after complex formation (Lu et al., 2019). A study about preparation of luteolin-phospholipid complexes found that the characteristic peaks of luteolin remained present (Xu et al., 2009). Hence, it is concluded that the chromophores of compounds are not affected by complexation with phospholipids.

8.5.2. Fourier transform infrared (FTIR) spectroscopic analysis

FTIR is an excellent approach for the structural analysis of phytosomes and provides information about various functional groups that indicate unique characteristics in the terms of band position, number, intensity and shape. The formulation of phytosomes have been reported to be proven by comparing spectrum of phytosomes with spectrum of physical mixtures of components. FTIR spectroscopy is considered a powerful tool to analyze the stability of phytosomes on incorporation in simple cosmetic gels or when micro dispersed in the water.

Different studies may indicate different results. Phytosomes loading rutin were prepared. The FTIR spectrum of the physical mixture and phytosomes was completely similar with that of pure rutin (Das and Kalita, 2014). FTIR spectrum confirmed that there was no involvement of functional groups in the preparation of Formononetin-phosphatidylcholine complexes (Agarwal et al., 2023). The FTIR spectrum of sinigrin phytosomes exhibited different peaks from pure sinigrin spectrum, phospholipid as well as their physical mixtures (Mazumder et al., 2016). FTIR spectrum of phytosomes co-loaded with curcumin and leflunomide was found to be significantly different from the spectra of curcumin, leflunomide and phospholipid, which indicated complex formation via hydrogen bonding (Nashaat et al., 2023). In another study, the formation of the silymarin-phospholipid phytosomal complex was confirmed by matching the FTIR spectrum of complex with the spectra of individual components utilized for the fabrication of phytosomes (Shriram et al., 2022).

8.5.3. Nuclear magnetic resonance (NMR)

The ^{1}H NMR and ^{13}C NMR techniques are important in the identification study of the complex structure. The chemical shift value, presence and absence of NMR peak of particular proton can be employed to characterize the

phytosome. The H-NMR Spectra showed the peak of tail portion of phospholipid molecule intact, revealing that the tail is not involved in any chemical interactions and serve to cover the envelope on the central choline-phytoactive portion of these complexes. The 13C-NMR is often performed for confirmation of the type of interaction involved for the complexation (Kumar et al., 2008). According to NMR, the formation of hydrogen bonds leads to linkage between phytoconstituents and phospholipids (Angelico et al., 2014). NMR study revealed the attachment of carbon (C-8) position of formononetin by replacing the quaternary amine of phospholipid to form formononetin-phospholipid complex (Agarwal et al., 2023).

8.5.4. Differential scanning calorimetry (DSC)

In DSC, interactions can be observed by comparing the transition temperature, appearance of new peaks, disappearance of original peaks, melting points, and changes in the relative peaks area. The crystallinity of the phytoactive ingredients is lost upon complexation, increasing the hydrophilicity of phytoconstituents. The crystalline bioactive compound shows a sharp peak at high melting point in DSC thermogram, while the phytosomes show a broad peak at a melting point significantly less than that of pure compound. The broad peak implies the loss of crystallinity and formation of phytosomal complex (Yue et al., 2008). In an investigation, sharp endothermal peaks of both silymarin and phospholipid were disappeared in the thermogram of the optimized silymarin-phospholipid complex and a new peak broad endothermal peak appeared at lower temperature. These results suggested that a stable silymarin-phospholipid complex was formed via hydrogen bonding, van der Waals interactions and/or weak intermolecular interactions between silymarin and phospholipid.

8.5.5. X-ray diffraction

X-ray diffraction (XRD) of active constituent, phospholipid, their physical mixtures and phyto-phospholipid complexes is usually performed and results are compared. X- ray diffraction of an active constituent and physical mixture indicates intense crystalline peaks showing a high crystal state, while phyto-phospholipid complexes do not show crystalline peak, suggesting amorphous form of constituents being complexed with phospholipids. That may be a reason behind the observation that phytosomal complexes have better lipophilicity and hydrophilicity than that of active constituents (Ghanbarzadeh et al., 2016). X-ray diffractogram study of the optimized silymarin phytosomes suggested that silymarin in the phytosomal formula is molecularly dispersed in a phospholipid matrix in an amorphous form (Shriram et al., 2022). Similar results were reported when the crystallinity of the cholinesterase inhibitor, huperzine A, changed from the crystalline state to the amorphous state upon complexation with phospholipids (Cai et al., 2012).

9. Advantages of phytosome technology

- Phytosomes exhibits an excellent feature such as better absorption which leads to better bioavailability than simple plant extracts (Bhise et al., 2019). An improved absorption leads to a lower dosage of phytoconstituents required for a biological effect (Barani et al., 2021).

- Phytosomes are cell-like where all the important constituents of plant extract are prevented from the degradation by gut bacteria and digestive secretions (Nagar, 2019). Formation of phytosomal complexes can also prevent

phytochemicals from degradation by the external conditions such as hydrolysis, oxidation, and photolysis (Kidd, 2009).

- Phytosomes exhibit better drug entrapment efficiency and stability because of chemical bonds between the bioactive compounds and phospholipid molecules. It makes sure proper drug delivery to the target tissues (Nagar, 2019).
- Phytosomes also exhibit nutritional benefits of the phospholipids (Karimi et al., 2015). Apart from serving as a carrier, the phosphatidylcholine employed in fabrication of phytosomes also serves as a hepato-protective agent leading to a synergistic effect when hepato-protective drugs are utilized. Phosphatidylcholine also nourishes the skin (Nagar, 2019).
- Phytosomes solubility in an aqueous medium is relatively less that ensures the formulation of stable creams or emulsions (Nagar, 2019).
- Du to enhanced absorption of bioactive phytochemicals across the skin, Phyto-phospholipid complexes are extensively employed in cosmetics due to their higher lipid profile and better skin penetration (Karimi et al., 2015).
- Phytosomes have higher rate drug complexation and also fabrication of phytosomes is not a complex process (Karimi et al., 2015). The methods of phytosomes preparation are simple, non-conventional and reproducible (Gaurav et al., 2021).
- Phytosomal complexation prolong the duration of drug. Frequent administration of the Naringenin is required due to its shorter half-time and rapid removal from the body. Phospholipid complexes of Naringenin were fabricated with motive to enhance its duration in blood circulatory system (Semalty et al., 2010). In another study, half-life of andrographolide–phospholipid complexes was incremented 3.34 times than that of pure andrographolide (Maiti et al., 2010).
- As the phytosomal complexes are biodegradable, drug entrapment is not an issue (Karimi et al., 2015).

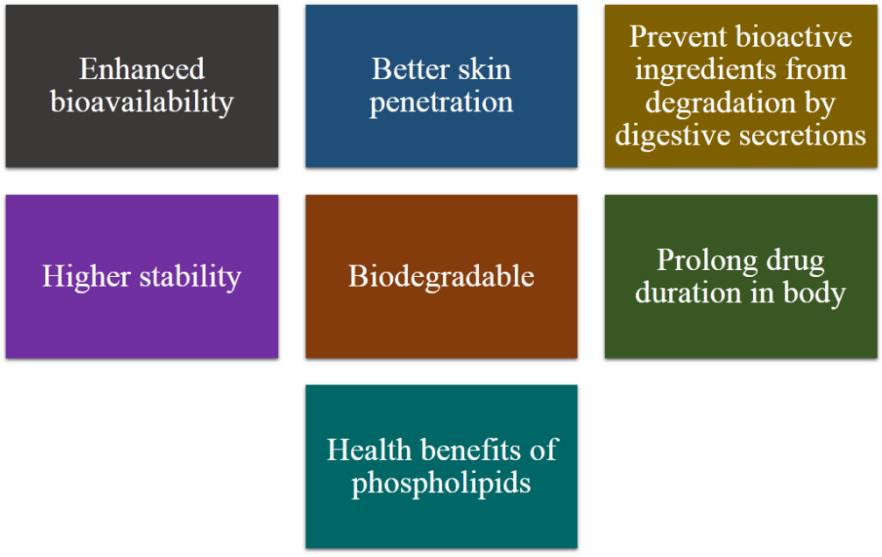

Figure 6. Advantages of phytosome technology

10. Limitations

- Despite of exhibiting a wide range of benefits as a drug delivery system, phytosomal products are not prevalent in the market.
- A major drawback of phytosome is the leaching of phytochemicals off the 'some' which decreases the desired concentration of drug which indicates their unstable nature (Chivte et al., 2017).
- It exhibits a short half-life.
- Hydrolysis, leakage, fusion and oxidation is undergone by phospholipid molecules.
- Its cost of production is high and allergic reactions to the phytosomal components may also be observed sometimes.
- Owing to their larger size, there may occur some problems while it is tried to target to the tissues (Dewan et al., 2016).
- Phospholipids (soy lecithin) can cause proliferation on MCF-7 cell lines of breast cancer (Gándola et al., 2014).

11. Marketed phytosomal products

Phytosomes are known to be an efficient nano-carrier drug delivery systems (Permana et al., 2020). The increased bioavailability of phytoconstituents, biological activities, and advantages of phytosome have been explored by various pharmaceutical industries (Barani et al., 2021). Some marketed phytosomes with their biological applications are given in table 2. Although, several phytosomal products are available in market, yet there are a lot of other phytochemicals with an outstanding ability to cure life threatening ailments, which have not been incorporated into phytosomes (Gaurav et al., 2021). Phytosome® and all other trademarks are owned by Indena S.p.A. Milan, Italy (Karimi et al., 2015).

Table 3. Phytosomes available in market (Patel et al., 2009; Karimi et al., 2015; Lu et al., 2019)

Sr. #	Trade name	Phytoconstituent complexed with phospholipid	Plant source	Applications
1.	Greenselect® phytosomes	Epigallocatechin 3-O-gallate	Green tea	An anticancer and antioxidant agent
2.	Leucoselect® phytosomes	Procyanidolic oligomers	Grape seeds	Anti-oxidant and anticancer
3.	Oleaselect™ phytosome	Polyphenolic compounds from essential oil of olives	*Olea europaea* L.	Prevent toxic oxidative reaction of low density lipoprotein cholesterol
4.	Casperome™	gum resin	*Banksia*	Improve tissue distribution of boswellic

			serrata	acids
5.	Hawthorn phytosome™	Flavonoids	Crataegus species	Antihypertensive and cardiotonic
6.	Curcumin (Merinoselect) phytosomes	Polyphenol	*Curcuma longa*	Anticancer and improve bioavailability of curcuminoids
7.	Sericoside phytosome	Sericoside	*Terminalia Sericea*	Anti-wrinkles and soothing effects
8.	*Ginkgoselect*®	24 % flavono-glycosides	*Ginkgo biloba*	Provide protection to vascular lining and brain.
9.	Mirtoselect® phytosome	Anthocyanosides	Bilberry	Decrease abnormal permeability of blood vessel and improve capillary tone. These have high potential in managing venous insufficiency and retinal blood vessel issues.
10.	Sabalselect® (Palmetto) phytosome	Saw palmetto berries extract	*Serenoa repens*	Helpful for prostate normal functioning
11.	Polinacea™ phytosome	Echinacosides	*Echinacea angustifolia*	It improves function of immune system in response to some toxic condition
12.	Lymphaselect™ phytosome	*Melilotus officinalis* standardized extract	*Melilotus officinalis*	It is suggested for venous diseases
13.	Panax ginseng phytosome	Ginsenosides	*Panax ginseng* roots	Utilized as a food product
14.	Zanthalene phytosome	Zanthalene	*Zanthoxylum bungeanum*	Anti-itching, anti-irritant, and soothing effects

12. Recent advanced research in phyto - phospholipids complexation

Various pharmaceutical manufacturers and researchers investigated the novelty and biological activities of phytosome formulations as well as the achieved the enhanced bioavailability of polar phytochemicals. The

researchers are encouraged to continue their field of research by the overall evidence for these formulations. Clinical research on the standardized products demonstrate greater efficiency as compared to unformulated extracts or phytochemicals will be important in the future to promote awareness of these technologies (Barani et al., 2021). Some plant extracts are getting more attention now a days due to their potent biological applications, such as, silymarin, grape seed extract, quercetin, curcumin, ginkgo biloba extract, etc. The efficacy of this technique and high demand of herbal medicines for numerous disease management, has paved the way of newer research. Various phytosomal formulations utilizing medicinal plants and phytochemicals have been reported since the development of the phytosome technology. A view of literature of a few of latest reported phytosomal formulations is given in table 3.

Table 4. Literature view of previous reported phytosomal formulations

Sr. #	Phytosomal formulations	Method employed for fabrication	Biological applications	References
1.	Quercetin loaded nano-phytosome	Thin layer hydration method	Anti-leishmania and antimalarial effects	(Hanif et al., 2023)
2.	Bergamot essential oil with spironolactone containing phytosomes	Thin film hydration technique	Treatment of acne vulgaris	(Albash et al., 2023)
3.	*Nicotiana tabacum* var. Virginia leaves extract loaded phytosomes	Solvent displacement method	Antioxidant and antiinflammatory activities	(Chittasupho et al., 2023)
4.	*Hedyotis corymbosa* L. extract loaded phytosomes	Phospholipid encapsulation	Enhanced delivery of extract for the efficient relief from neuropathic pain	(Kumar et al., 2023)
5.	Phytosomes containing carotenoids of *Nyctanthes arbor-tristis* and *Tagetes patula*	Lipid film hydration technique	Protect skin aging induced due to D-galactose	(Naik et al., 2023)
6.	Phytosomes of Parthenolide	Solvent evaporation method	Parthenolide containing phytosomes attenuate the renal dysfunction and also structural damage by decreasing inflammation, oxidative stress, and apoptosis in kidney.	(Albalawi et al., 2023)
7.	Genistein phytosome	Solvent evaporation method	Breast cancer treatment	(Komeil et al., 2022)

8.	Scorpion venom-standardized quercetin loaded phytosomal complexes	Anti-solvent precipitation	Anticancer activity against MCF-7 Cells in breast cancer management	(Alhakamy et al., 2022)
9.	Silybin loaded phytosome	Solvent evaporation method	Neuro-protective activity and attenuates cerebral ischemia-reperfusion injury	(Pasala et al., 2022)
10.	Polyphenols from *Moringa oleifera* leaf loaded phytosome	Nano-precipitation method	Treatment against cell lines of breast cancer	(Wanjiru et al., 2022)
11.	*Geophila repens* phytosome loaded intranasal gel formulation	Co-solvency method	Efficient treatment of Alzheimer's disease	(Rajamma et al., 2022)
12	Phytosome of *Punica granatum* L. peel extract	Thin film hydration method	Anti-infective, antimicrobial, anti-oxidative, antidiarrheal, hepato-protection, anti-atherogenicity and anti-inflammation therapy	(Kazemi et al., 2022)
13.	Novel diammonium glycyrrhizinate containing phytosome	Solvent evaporation technique	Induce nasal immune responses	(Chen et al., 2022)
14.	*Intsia bijuga* heartwood extract loaded phytosome	Solvent evaporation technique	Serve as an antioxidant, tyrosinase inhibitor and sun protector	(Sari et al., 2021)
15.	Phytosomes of *Aloe vera* extract	Phospholipid encapsulation	Anticancer activity	(Murugesan et al., 2021)
16.	Leucoselect phytosome containing grape seed procyanidin extract	Phospholipid complexation	Antineoplastic and anti-inflammatory activity	(Mao et al., 2021)
17.	Phytosome loading allicin-rich extract	Solvent evaporation technique	Extensive pharmacological activities including antihypertensive, antioxidant,	(Nining et al., 2021)

			cardioprotective, antimicrobial, antidiabetic, nephroprotective, anti-carcinogenic and a cytochrome activity.	
18.	*Centella asiatica* L. phytosomes	Phytosome complexation	Antioxidant and anti-inflammatory activity; Promoting Bdnf expression leading to improvement of cognitive action	(Sbrini et al., 2020)
19.	*Trigonella foenum-graecum phytosomes*	Thin film hydration technique	Anti-Inflammatory and anti-arthritic activity	(Sharma et al., 2020)
20.	Naringenin-loaded Dipalmitoylphosphatidylcholine phytosomes	Solvent evaporation and a freeze-drying method	Utilized in the inhaled treatment of mild lung damage	(Yu et al., 2020)
21.	Icariin containing phytosomes	Anti-solvent precipitation	Incremented cytotoxicity against ovarian cancer cells	(Alhakamy et al., 2020)
22.	Thymoquinone loaded phytosomes	Refluxing in combination with anti-solvent precipitation	Anticancer effects against human cells of lung cancer	(Alhakamy et al., 2020)
23.	Selenium-deposited tripterine phytosomes	*In situ* reduction technique or melting-hydration	Boost the anti-arthritic effectiveness a synergistic sensitization	(Zhu et al., 2020)
24.	Cocoa pod husk containing phytosomes	Thin-layer method	Antioxidant and tyrosinase inhibitory effects	(Priani et al., 2019)
25.	Phytosomes containing ethanolic extract of *Bombax ceiba* leaves	Anti-solvent precipitation technique	Hepato-protective activity	(Karole and Gupta, 2019)
26.	Chrysin-loaded phytosomes	Solvent evaporation method	Enhanced solubility and improved glucose uptake in C2-C12 muscle cells.	(Kim et al., 2019)
27.	*Diospyros kaki* L. extract containing phytosomes	Phytosomal complexation	Helpful in reducing oxidative degradation caused due to the reactive oxygen species	(Direito et al., 2019)

28.	Diosgenin derivative loaded phytosomes	Thin-film rehydration method	Anticancer action against lung cancer cells	(Xu et al., 2019)
29.	Phytosomes loading aqueous extract of *Annona muricata* L.	Phytosome complexation	*In vivo* depression treatment	(Mancini et al., 2018)
30.	*Vitis vinifera* L. seed extract Phytosome	Thin layer hydration method	Improved drug penetration of in serum dosage form	(Surini et al., 2018)
31.	Curcumin loaded phytosomes	Solvent evaporation method	Helpful in the treatment against human diseases including cancer, retinopathy, diabetic microangiopathy osteoarthritis, and inflammatory diseases	(Mirzaei et al., 2017) (Allam et al., 2015)
32.	Phytosomes containing methanolic extract of *Aegle marmelos* leaves	Solvent evaporation method	Antioxidant, anti-proliferative and anticancer effects	(Dhase and Saboo, 2015)

13. Conclusion

Phytosome is an innovative emerging technique commonly applied to the plant based pharmaceuticals which have phytochemicals of plant extract surrounded by phospholipid mostly bioactive compounds of herbal medicine are water soluble such as flavonoids. As compared to the traditional herbal extract, phytosome shows high absorption leading to better bioavailability owing to its lipid soluble outer-layer. Apart from that, the phospholipids utilized possess their own therapeutic benefits for the body. The methods for formulation of phytosomes are simple, non-conventional, and reproducible. Numerous patents and marketed formulations are already approved for innovative formulations, processes and applications of phytosomes. Many phytochemicals have been successfully encapsulated as phytosomes and it is anticipated that further phytochemicals may benefit from similar formulations. Future research may find synergistic benefits when phytosomes are combined with other phytochemicals or when a drug and a phytochemical are combined in a nano-vesicle. The utilization of phytosomes encapsulated with other phytoconstituents or the combination of a medicine and a phytochemical in a nano-vesicle could have stimulatory effects in future study.

14. Future Outlook

The development of phytosome nanotechnology has the potential to have an impact on medicine delivery and could completely change the way topical bioactive phytochemicals are currently delivered. The phytosomes as lipid-based nanocarriers facilitate the increase of the pharmacokinetic and pharmacodynamic properties of polyphenolic chemicals derived from herbs that make this nanotechnology a promising tool for the creation of novel topical formulations. Due to their distinct physiochemical properties, the use of this nano-sized delivery

system could increase the penetration of phytochemicals across biological barriers, enhancing their bioavailability (Alharbi et al., 2021).

Initially, phytosomes were employed in cosmetics, now are frequently used in the treatment of cancer, tumors, inflammation, heart disease, and other liver-related illnesses. With this newly created formulation tool, Phytosomes has re-explained the significance of herbals in modern drug targeting tactics. Owing to binding specific ligands and antigens to the cellular structures, phyto-phospholipid complexes can also be strong candidates for active targeting in addition to passive targeting. As a result, more diseases, such as osteoarthritis, cancer, and rheumatism, can be treated with phyto-phospholipid complexes. The dimension of the product can be changed to a variety of limited ranges by utilizing more advanced approaches, such as supercritical fluid systems, and optimizing the pressure, temperature, and various other factors. Because of their improved penetration and better retention, controlled size, products will be applicable in targeting different areas such as tumors and inflammation more efficiently. In order to achieve the best drug release profile and the highest level of entrapment efficiency, various variables such as the molar ratios of phytoactive or drug with phospholipids, temperature and other variables, can be optimized employing various statistical tools such as *Box–Behnken design*, factorial design and others (Khan et al., 2013).

Phospholipids considerably increase bioavailability as compared to chemically similar non-complexed form. With the help of physicians and researchers, the phyto-phospholipid complex has a promising future for its application in the pharmaceutical industry (Lu et al., 2019). This may open up a big window of opportunity to use this approach for other medicinal purposes. Indeed, encapsulating potential phytochemicals like curcumin with efficient drug delivery techniques may open an approach for the development of eco-friendly and safe treatments for the common human disorders. The ingestion of whole curcumin nano-phytosomes for the targeted delivery to different organs, including malignancies, is an important area to be investigated (Ipar et al., 2019).

A few of nano-technology based drug delivery systems for the treatment of cancer have received FDA approval. Lipid based nano-vesicles are one of new nanocarriers, having many significance as compared to traditional drug carriers, particularly in terms of bioavailability, biocompatibility, affordability, biodegradability and raw material accessibility, with a long history of research. Phytosomal delivery systems for cancer therapy are expected to be advanced by incorporating natural and synthetic anti-cancer substances into nano-phytosomes. The use of phytosome technology in the formulation of nutraceuticals can be potentially revolutionize as the hydrophilic phytochemicals are employed in cancer treatment (Babazadeh et al., 2018).

Phytosome technology offers a wide range of benefits as compared to other conventional dosage forms. There are several pharmaceutical phytosomes with registered patents in the market. This research demonstrates that Phytosomes® have introduced a new dimension to pharmaceutical research and development, with a treasure of untapped potential (Agarwal et al., 2012). As far as the potential of phytosome technology is concerned, it has a great future for use in formulation technology and applications of hydrophilic plant compounds.

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Competing Interests Statement

The author has declared no competing interests.

Consent for Publication

The author declares that she consented to the publication of this study.

Ethical Approval

Not applicable.

Author's Contribution

Author's independent contribution.

References

Abdul Rasool, B.K., N. Al Mahri, N. Alburaimi, F. Abdallah & A.S.B. Shamma (2022). A narrative review of the potential roles of lipid-based vesicles (vesiculosomes) in burn management. Scientia Pharmaceutica, 90: 39. https://doi.org/10.3390/scipharm90030039.

Agarwal, A., P. Chakraborty, D.D. Chakraborty & V.A. Saharan (2012). Phytosomes: complexation, utilisation and commerical status. Journal of Biologically Active Products from Nature, 2: 65-77. https://doi.org/10.1080/22311866.2012.10719111.

Agarwal, A., M. Wahajuddin, S. Chaturvedi, S.K. Singh, M. Rashid, R. Garg, D. Chauhan, N. Sultana & J.R. Gayen (2023). Formulation and characterization of phytosomes as drug delivery system of formononetin: an effective anti-osteoporotic agent. Current Drug Delivery. https://doi.org/10.2174/1567201820666230124114906.

Albalawi, R.S., L.S. Binmahfouz, R.H. Hareeri, R.A. Shaik & A.M. Bagher (2023). Parthenolide phytosomes attenuated gentamicin-induced nephrotoxicity in rats via activation of Sirt-1, Nrf2, OH-1, and NQO1 Axis. Molecules, 28: 2741. https://doi.org/10.3390/molecules28062741.

Albash, R., N.M. Badawi, M.I. Hamed, M.H. Ragaie, S.S. Mohammed, R.M. Elbesh, K.M. Darwish, M.O. Lashkar, S.S. Elhady & S. Mosallam (2023). Exploring the synergistic effect of bergamot essential oil with spironolactone loaded nano-phytosomes for treatment of acne vulgaris: In vitro optimization, in silico studies, and clinical evaluation. Pharmaceuticals, 16: 128. https://doi.org/10.3390/ph16010128.

Alhakamy, N.A., U.A. Fahmy, S.M. Badr-Eldin, O.A. Ahmed, H.Z. Asfour, H.M. Aldawsari, M.M. Algandaby, B.G. Eid, A.B. Abdel-Naim & Z.A. Awan (2020). Optimized icariin phytosomes exhibit enhanced cytotoxicity and apoptosis-inducing activities in ovarian cancer cells. Pharmaceutics, 12: 346. https://doi.org/10.3390/pharmaceutics12040346.

Alhakamy, N.A., S.M. Badr-Eldin, U.A. Fahmy, N.K. Alruwaili, Z.A. Awan, G. Caruso, M.A. Alfaleh, A.L. Alaofi, F.O. Arif & O.A. Ahmed (2020). Thymoquinone-loaded soy-phospholipid-based phytosomes exhibit anticancer potential against human lung cancer cells. Pharmaceutics, 12: 761. https://doi.org/10.3390/pharmaceutics12080761.

Alhakamy, N.A., U.A. Fahmy, S.M.B. Eldin, O.A.Ahmed, H.M. Aldawsari, S.Z. Okbazghi, M.A. Alfaleh, W.H. Abdulaal, A.J. Alamoudi & F.M. Mady (2022). Scorpion venom-functionalized quercetin phytosomes for breast cancer management: in vitro response surface optimization and anticancer activity against MCF-7 cells. Polymers, 14: 93. https://doi.org/10.3390/polym14010093.

Alharbi, W.S., F.A. Almughem, A.M. Almehmady, S.J. Jarallah, W.K. Alsharif, N.M. Alzahrani & A.A. Alshehri (2021). Phytosomes as an emerging nanotechnology platform for the topical delivery of bioactive phytochemicals. Pharmaceutics, 13: 1475. https://doi.org/10.3390/pharmaceutics13091475.

Allam, A.N., I.A. Komeil & O.Y. Abdallah (2015). Curcumin phytosomal softgel formulation: Development, optimization and physicochemical characterization. Acta Pharmaceutica, 65: 285-297. https://doi.org/10.1515/acph-2015-0029.

Angelico, R., A. Ceglie, P. Sacco, G. Colafemmina, M. Ripoli & A. Mangia (2014). Phyto-liposomes as nanoshuttles for water-insoluble silybin–phospholipid complex. International Journal of Pharmaceutics, 471: 173-181. https://doi.org/10.1016/j.ijpharm.2014.05.026.

Anjana, R., S. Kumar, H. Sharma & R. Khar (2017). Phytosome drug delivery of natural products: A promising technique for enhancing bioavailability. International Journal of Drug Delivery Technology, 7: 157-165.

Babazadeh, A., M. Zeinali & H. Hamishehkar (2018). Nano-phytosome: a developing platform for herbal anti-cancer agents in cancer therapy. Current Drug Targets, 19: 170-180. https://doi.org/10.2174/1389450118666170508095250.

Barani, M., E. Sangiovanni, M. Angarano, M.A. Rajizadeh, M. Mehrabani, S. Piazza, H.V. Gangadharappa, A. Pardakhty, M. Mehrbani & M. Dell'Agli (2021). Phytosomes as innovative delivery systems for phytochemicals: A comprehensive review of literature. International Journal of Nanomedicine, Pages 6983-7022. https://doi.org/10.2147/IJN.S318416.

Bhise, J.J., O.G. Bhusnure, S.R. Jagtap, S.B. Gholve & R.R. Wale (2019). Phytosomes: a novel drug delivery for herbal extracts. Journal of Drug Delivery and Therapeutics, 9: 924-930. https://doi.org/10.22270/jddt.v9i3-s.2863.

Bresciani, L., G. Di Pede, C. Favari, L. Calani, V. Francinelli, A. Riva, G. Petrangolini, P. Allegrini, P. Mena & D. Del Rio (2021). In vitro (poly) phenol catabolism of unformulated-and phytosome-formulated cranberry (*Vaccinium macrocarpon*) extracts. Food Research International, 141: 110137. https://doi.org/10.1016/j.foodres.2021.110137.

Cai, X., Y. Luan, Y. Jiang, A. Song, W. Shao, Z. Li & Z. Zhao (2012). Huperzine A-phospholipid complex-loaded biodegradable thermosensitive polymer gel for controlled drug release. International Journal of Pharmaceutics, 433: 102-111. https://doi.org/10.1016/j.ijpharm.2012.05.009.

Carignani, E., M. Geppi, M. Lovati, E. de Combarieu & S. Borsacchi (2020). Solid State NMR study of the mixing degree between *Ginkgo biloba* extract and a soy-lecithin-phosphatidylserine in a composite prepared by the phytosome® method. Chemistry Africa, 3: 717-725. https://link.springer.com/article/10.1007/s42250-020-00165-0.

Chauhan, N.S., R. Gowtham & B. Gopalkrishna (2009). Phytosomes: a potential phyto-phospholipid carriers for herbal drug delivery. J Pharm Res, 2: 1267-1270. https://citeseerx.ist.psu.edu/document?repid=rep1&type=pdf&doi=4bffd703d68aa66f42d48117dfe4d056c665e790.

Chen, X., X. Fan & F. Li (2022). Development and Evaluation of a Novel Diammonium Glycyrrhizinate Phytosome for Nasal Vaccination. Pharmaceutics, 14: 2000. https://doi.org/10.3390/pharmaceutics14102000.

Chittasupho, C., K. Chaobankrang, A. Sarawungkad, W. Samee, S. Singh, K. Hemsuwimon, S. Okonogi, K. Kheawfu, K. Kiattisin & W. Chaiyana (2023). Antioxidant, anti-inflammatory and attenuating intracellular reactive oxygen species activities of *Nicotiana tabacum* var. *Virginia* Leaf extract phytosomes and shape memory gel formulation. Gels, 9: 78. https://doi.org/10.3390/gels9020078.

Chivte, P.S., V.S. Pardhi, V.A. Joshi & A. Rani (2017). A review on therapeutic applications of phytosomes. Journal of Drug Delivery and Therapeutics, 7: 17-21. https://doi.org/10.22270/jddt.v7i5.1513.

Das, M.K. & B. Kalita (2014). Design and evaluation of phyto-phospholipid complexes (phytosomes) of rutin for transdermal application. Journal of Applied Pharmaceutical Science, 4: 051-057. http://dx.doi.org/10.7324/JAPS.2014.401010.

Dewan, N., D. Dasgupta, S. Pandit & P. Ahmed (2016). Review on-Herbosomes, A new arena for drug delivery. Journal of Pharmacognosy and Phytochemistry, 5: 104. https://www.phytojournal.com/archives/2016.v5.i4.902/review-on-herbosomes-a-new-arena-for-drug-delivery.

Dhase, A.S., & S.S. Saboo (2015). Preparation and evaluation of phytosomes containing methanolic extract of leaves of *Aegle marmelos* (bael). International Journal of Pharm Tech Research, 8: 231-240. http://www.sphinxsai.com/2015/ph_vol8_no6/2/(231-240)V8N6PT.pdf.

Direito, R., C. Reis, L. Roque, M. Gonçalves, A. Sanches-Silva, M.M. Gaspar, R. Pinto, J. Rocha, B. Sepodes & M. Rosário Bronze (2019). Phytosomes with persimmon (*Diospyros kaki* L.) extract: Preparation and preliminary demonstration of in vivo tolerability. Pharmaceutics, 11: 296. https://doi.org/10.3390/pharmaceutics11060296.

Dongare, P.N., A.S. Motule, M.R. Dubey, M.P. More, P.A. Patinge, R.L. Bakal & J.V. Manwar (2021). Recent development in novel drug delivery systems for delivery of herbal drugs: An updates. GSC Advanced Research and Reviews, 8: 008-018. https://doi.org/10.30574/gscarr.2021.8.2.0158.

Freag, M.S., Y.S. Elnaggar & O.Y. Abdallah (2013). Lyophilized phytosomal nanocarriers as platforms for enhanced diosmin delivery: optimization and ex vivo permeation. International Journal of Nanomedicine, Pages 2385-2397. https://doi.org/10.2147/IJN.S45231.

Gándola, Y.B., S.E. Pérez, P.E. Irene, A.I. Sotelo, J.G. Miquet, G.R. Corradi, A.M. Carlucci & L. Gonzalez (2014). Mitogenic effects of phosphatidylcholine nanoparticles on MCF-7 breast cancer cells. BioMed Research International. https://doi.org/10.1155/2014/687037.

Gaurav, V., S. Paliwal, A. Singh, S. Pandey & M. Aqil (2021). Phytosomes: Preparation, evaluation and application. Int J Res Eng Sci, 9: 35-39.

Ghanbarzadeh, B., A. Babazadeh & H. Hamishehkar (2016). Nano-phytosome as a potential food-grade delivery system. Food bioscience, 15: 126-135. https://doi.org/10.1016/j.fbio.2016.07.006.

Habbu, P., S. Madagundi, R. Shastry, R. Vanakudri & V. Kulkarni (2015). Preparation and evaluation of antidiabetic activity of *Allium cepa*-phospholipid complex (phytosome) in streptozotocin induced diabetic rats. RGUHS J Pharm Sci, 5: 132-141.

Hammam, E., J. Basahi, I. Ismail, I. Hassan & T. Almeelbi (2017). The role of hydrogen bonding in the fluorescence quenching of 2, 6-bis ((E)-2-(benzoxazol-2-yl) vinyl) naphthalene (BBVN) in methanol. Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy, 173: 681-686. https://doi.org/10.1016/j.saa.2016.10.018.

Hanif, H., V. Abdollahi, F. Javani Jouni, M. Nikoukar, B. Rahimi Esboei & E. Shams (2023). Quercetin nano phytosome: as a novel anti-leishmania and anti-malarial natural product. Journal of Parasitic Diseases, Pages 1-8. https://link.springer.com/article/10.1007/s12639-022-01561-8.

Hou, Z., Y. Li, Y. Huang, C. Zhou, J. Lin, Y. Wang, F. Cui, S. Zhou, M. Jia & S. Ye (2013). Phytosomes loaded with mitomycin C–soybean phosphatidylcholine complex developed for drug delivery. Molecular pharmaceutics, 10: 90-101. https://doi.org/10.1021/mp300489p.

Ipar, V.S., A. Dsouza & P.V. Devarajan (2019). Enhancing curcumin oral bioavailability through nano formulations. European Journal of Drug Metabolism and Pharmacokinetics, 44: 459-480. https://link.springer.com/article/10.1007/s13318-019-00545-z.

Islam, N., M. Irfan, T. Hussain, M. Mushtaq, I.U. Khan, A.M. Yousaf, M.U. Ghori & Y. Shahzad (2022). Piperine phytosomes for bioavailability enhancement of domperidone. Journal of Liposome Research, 32: 172-180. https://doi.org/10.1080/08982104.2021.1918153

Jahangir, M.A., C. Anand, A. Muheem, S.J. Gilani, M. Taleuzzaman, A. Zafar, M. Jafar, S. Verma & M. Barkat (2020). Nano phytomedicine based delivery system for CNS disease. Current Drug Metabolism, 21: 661-673. https://doi.org/10.2174/1389200221666200523161003.

Karataş, A., & F. Turhan (2015). Phyto-phospholipid complexes as drug delivery system for herbal extracts/molecules. Turkish Journal of Pharmaceutical Sciences, 12: 93-102.

Karimi, N., B. Ghanbarzadeh, H. Hamishehkar, F. Keyvani, A. Pezeshki & M.M. Gholian (2015). Phytosome and liposome: the beneficial encapsulation systems in drug delivery and food application. https://www.sid.ir/en/VEWSSID/J_pdf/50003520150306.pdf.

Karole, S., & G. Gupta (2019). Preparation and evaluation of phytosomes containing ethanolic extract of leaves of *Bombax ceiba* for hepatoprotective activity. Evaluation, 6: 1-5.

Kattyar, S.L., P.S. Patil, S.V. Patil & S.S. Kadam (2022). Phytosomes and recent research on phytosomal drugs. Asian Journal of Pharmaceutical Analysis, 12: 61-69. http://dx.doi.org/10.52711/2231-5675.2022.00012.

Kazemi, D., S.N. Ebrahimi & R.M. Kouchaksaraee (2022). Fabrication and optimization of physicochemical properties of nano-phytosome from *Punica granatum* L. peel enriched polyphenol extract. Journal of Medicinal Plants, 21: 50-61. https://jmp.ir/article-1-3385-fa.pdf.

Khan, J., A. Alexander, S. Saraf & S. Saraf (2013). Recent advances and future prospects of phyto-phospholipid complexation technique for improving pharmacokinetic profile of plant actives. Journal of Controlled Release, 168: 50-60. https://doi.org/10.1016/j.jconrel.2013.02.025.

Kidd, P.M. (2009). Bioavailability and activity of phytosome complexes from botanical polyphenols: the silymarin, curcumin, green tea, and grape seed extracts. Altern Med Rev, 14: 226-246.

Kim, S.-M., J.-I. Jung, C. Chai & J.-Y. Imm (2019). Characteristics and glucose uptake promoting effect of chrysin-loaded phytosomes prepared with different phospholipid matrices. Nutrients, 11: 2549. https://doi.org/10.3390/nu11102549.

Komeil, I.A., O.Y. Abdallah & W.M. El-Refaie (2022). Surface modified genistein phytosome for breast cancer treatment: In-vitro appraisal, pharmacokinetics, and in-vivo antitumor efficacy. European Journal of Pharmaceutical Sciences, 179: 106297. https://doi.org/10.1016/j.ejps.2022.106297.

Kumar, M., M. Ahuja & S.K. Sharma (2008). Hepatoprotective study of curcumin-soya lecithin complex. Scientia Pharmaceutica, 76: 761-774. https://doi.org/10.3797/scipharm.0808-09.

Kumar, N., R. Goel, M. Singh, N.K. Sharma, P.K. Gaur & P.K. Sharma (2023). Development and evaluation of *Hedyotis corymbosa* (L.) extract containing Phytosomes: A preclinical approach for treatment of neuropathic pain in Rodent model. Journal of Microencapsulation, Pages 1-16. https://doi.org/10.1080/02652048.2023.2188938.

Li, J., X. Wang, T. Zhang, C. Wang, Z. Huang, X. Luo & Y. Deng (2015). A review on phospholipids and their main applications in drug delivery systems. Asian Journal of Pharmaceutical Sciences, 10: 81-98. https://doi.org/10.1016/j.ajps.2014.09.004.

Li, Y., D.-J. Yang, S.-L. Chen, S.-B. Chen & A.S.-C. Chan (2008). Process parameters and morphology in puerarin, phospholipids and their complex microparticles generation by supercritical antisolvent precipitation. International Journal of Pharmaceutics, 359: 35-45. https://doi.org/10.1016/j.ijpharm.2008.03.022.

Lu, M., Q. Qiu, X. Luo, X. Liu, J. Sun, C. Wang, X. Lin, Y. Deng & Y. Song (2019). Phyto-phospholipid complexes (phytosomes): A novel strategy to improve the bioavailability of active constituents. Asian Journal of Pharmaceutical Sciences, 14: 265-274. https://doi.org/10.1016/j.ajps.2018.05.011.

Maiti, K., K. Mukherjee, V. Murugan, B.P. Saha & P.K. Mukherjee (2010). Enhancing bioavailability and hepatoprotective activity of andrographolide from *Andrographis paniculata*, a well-known medicinal food, through its herbosome. Journal of the Science of Food and Agriculture, 90: 43-51. https://doi.org/10.1002/jsfa.3777.

Mancini, S., L. Nardo, M. Gregori, I. Ribeiro, F. Mantegazza, C. Delerue-Matos, M. Masserini & C. Grosso (2018). Functionalized liposomes and phytosomes loading *Annona muricata* L. aqueous extract: Potential nanoshuttles for

brain-delivery of phenolic compounds. Phytomedicine, 42: 233-244. https://doi.org/10.1016/j.phymed.2018.03.053.

Mao, J.T., B. Xue, S. Fan, P. Neis, C. Qualls, L. Massie & O. Fiehn (2021). Leucoselect phytosome modulates serum eicosapentaenoic acid, docosahexaenoic acid, and prostaglandin E3 in a phase i lung cancer chemoprevention study effects of grape seed extract on complex lipid metabolomics. Cancer Prevention Research, 14: 619-626. https://doi.org/10.1158/1940-6207.CAPR-20-0585.

Maryana, W., H. Rachmawati & D. Mudhakir (2016). Formation of phytosome containing silymarin using thin layer-hydration technique aimed for oral delivery. Materials Today: Proceedings, 3: 855-866. https://doi.org/10.1016/j.matpr.2016.02.019.

Mazumder, A., A. Dwivedi, J.L. Du Preez & J. Du Plessis (2016). In vitro wound healing and cytotoxic effects of sinigrin–phytosome complex. International Journal of Pharmaceutics, 498: 283-293. https://doi.org/10.1016/j.ijpharm.2015.12.027.

Metkari, V., R. Shah, N. Salunkhe & S. Gurav (2023). QBD approach for the design, optimization, development, and characterization of Naringenin-loaded phytosomes to enhance solubility and oral bioavailability. Journal of Pharmaceutical Innovation, Pages 1-15. https://link.springer.com/article/10.1007/s12247-023-09775-w.

Mirzaei, H., A. Shakeri, B. Rashidi, A. Jalili, Z. Banikazemi & A. Sahebkar (2017). Phytosomal curcumin: A review of pharmacokinetic, experimental and clinical studies. Biomedicine & Pharmacotherapy, 85: 102-112. https://doi.org/10.1016/j.biopha.2016.11.098.

Mishra, Y., H.I.M. Amin, V. Mishra, M. Vyas, P.K. Prabhakar, M. Gupta, R. Kanday, K. Sudhakar, S. Saini & A. Hromić-Jahjefendić (2022). Application of nanotechnology to herbal antioxidants as improved phytomedicine: An expanding horizon. Biomedicine & Pharmacotherapy, 153: 113413. https://doi.org/10.1016/j.biopha.2022.113413.

Murugesan, M.P., M.V. Ratnam, Y. Mengitsu & K. Kandasamy (2021). Evaluation of anti-cancer activity of phytosomes formulated from *Aloe vera* extract. Materials Today: Proceedings, 42: 631-636. https://doi.org/10.1016/j.matpr.2020.11.047.

Nagar, G. (2019). Phytosomes: a novel drug delivery for herbal extracts. Int J Pharm Sci Res., Pages 949-959. http://www.rjlbpcs.com/article-pdf-downloads/2019/26/610.pdf.

Naik, A.A., C.H. Gadgoli & A.B. Naik (2023). Formulation containing phytosomes of carotenoids from *Nyctanthes arbor-tristis* and *Tagetes patula* protect D-galactose Induced skin aging in mice. Clinical Complementary Medicine and Pharmacology, 3: 100070. https://doi.org/10.1016/j.ccmp.2022.100070.

Naik, G.G., M.B. Alam, V. Pandey, P.K. Dubey, A.S. Parmar & A.N. Sahu (2020). Pink fluorescent carbon dots derived from the phytomedicine for breast cancer cell imaging. ChemistrySelect, 5: 6954-6960. https://doi.org/10.1002/slct.202001613.

Nashaat, D., M. Elsabahy, K.M. Hassanein, G.A. El-Gindy & E.H. Ibrahim (2023). Development and in vivo evaluation of therapeutic phytosomes for alleviation of rheumatoid arthritis. International Journal of Pharmaceutics, 644: 123332. https://doi.org/10.1016/j.ijpharm.2023.123332.

Nazari, M., H. Majdi, M. Milani, S. Abbaspour-Ravasjani, H. Hamishehkar & L.-T. Lim (2019). Cinnamon nanophytosomes embedded electrospun nanofiber: Its effects on microbial quality and shelf-life of shrimp as a novel packaging. Food Packaging and Shelf Life, 21: 100349. https://doi.org/10.1016/j.fpsl.2019.100349.

Pasala, P.K., R.K. Uppara, et al. (2022). Silybin phytosome attenuates cerebral ischemia-reperfusion injury in rats by suppressing oxidative stress and reducing inflammatory response: In vivo and in silico approaches. Journal of Biochemical and Molecular Toxicology, 36: e23073. https://doi.org/10.1002/jbt.23073.

Patel, J., R. Patel, K. Khambholja & N. Patel (2009). An overview of phytosomes as an advanced herbal drug delivery system. Asian J Pharm Sci, 4: 363-371.

Pathan, R.A., & U. Bhandari (2011). Preparation & characterization of embelin–phospholipid complex as effective drug delivery tool. Journal of Inclusion Phenomena and Macrocyclic Chemistry, 69: 139-147. https://link.springer.com/article/10.1007/s10847-010-9824-2.

Permana, A.D., R.N. Utami, A.J. Courtenay, M.A. Manggau, R.F. Donnelly & L. Rahman (2020). Phytosomal nanocarriers as platforms for improved delivery of natural antioxidant and photoprotective compounds in propolis: An approach for enhanced both dissolution behaviour in biorelevant media and skin retention profiles. Journal of Photochemistry and Photobiology B: Biology, 205: 111846. https://doi.org/10.1016/j.jphotobiol.2020.111846.

Priani, S.E., S. Aprilia, R. Aryani & L. Purwanti (2019). Antioxidant and tyrosinase inhibitory activity of face serum containing cocoa pod husk phytosome (*Theobroma cacao* L.). Journal of Applied Pharmaceutical Science, 9: 110-115. http://dx.doi.org/10.7324/JAPS.2019.91015.

Rahman, H.S., H.H. Othman, N.I. Hammadi, S.K. Yeap, K.M. Amin, N. Abdul Samad & N.B. Alitheen (2020). Novel drug delivery systems for loading of natural plant extracts and their biomedical applications. International Journal of Nanomedicine, Pages 2439-2483. https://doi.org/10.2147/IJN.S227805.

Rahman, S.H. (2021). Formulation and evaluation of *Cassia auriculata* flower extract-loaded phytosomal cream to enhance the topical bioavailability. International Journal of Green Pharmacy (IJGP), Page 15.

Rajamma, S.S., V. Krishnaswami, S.L. Prabu & R. Kandasamy (2022). *Geophila repens* phytosome-loaded intranasal gel with improved nasal permeation for the effective treatment of Alzheimer's disease. Journal of Drug Delivery Science and Technology, 69: 103087. https://doi.org/10.1016/j.jddst.2021.103087.

Sari, R.K., Y.H. Prayogo, R.A.L. Sari, N. Asidah, M. Rafi, I. Wientarsih & W. Darmawan (2021). *Intsia bijuga* Heartwood Extract and Its Phytosome as Tyrosinase Inhibitor, Antioxidant, and Sun Protector. Forests, 12: 1792. https://doi.org/10.3390/f12121792.

Sbrini, G., P. Brivio, M. Fumagalli, F. Giavarini, D. Caruso, G. Racagni, M. Dell'Agli, E. Sangiovanni & F. Calabres (2020). *Centella asiatica* L. Phytosome improves cognitive performance by promoting BDNF expression in rat prefrontal cortex. Nutrients, 12: 355. https://doi.org/10.3390/nu12020355.

Semalty, A. (2014). Cyclodextrin and phospholipid complexation in solubility and dissolution enhancement: a critical and meta-analysis. Expert Opinion on Drug Delivery, 11: 1255-1272. https://doi.org/10.1517/17425247.2014.916271.

Semalty, A., M. Semalty, D. Singh & M. Rawat (2010). Preparation and characterization of phospholipid complexes of naringenin for effective drug delivery. Journal of Inclusion Phenomena and Macrocyclic Chemistry, 67: 253-260. https://link.springer.com/article/10.1007/s10847-009-9705-8.

Semalty, A., M. Semalty, D. Singh & M. Rawat (2012). Phyto-phospholipid complex of catechin in value added herbal drug delivery. Journal of Inclusion Phenomena and Macrocyclic Chemistry, 73: 377-386. https://link.springer.com/article/10.1007/s10847-011-0074-8.

Sharma, N., S. Singh, N. Laller & S. Arora (2020). Application of central composite design for statistical optimization of *Trigonella foenum-graecum* phytosome-based cream. Research Journal of Pharmacy and Technology, 13: 1627-1632.

Sharma, S., & A.N. Sahu (2016). Development, characterization, and evaluation of hepatoprotective effect of *Abutilon indicum* and *Piper longum* phytosomes. Pharmacognosy Research, 8: 29. https://doi.org/10.4103%2F0974-8490.171102.

Shende, M.A., M.S. More & R.P. Marathe (2018). Development and evaluation of *Terminalia Arjuna* loaded phytosome for bioavailability enhancement. International Journal of Pharmaceutical Sciences and Nanotechnology, 11: 4012-4020. https://doi.org/10.37285/ijpsn.2018.11.2.2.

Shirsath, N.R., & A.K. Goswami (2019). Nanocarriers based novel drug delivery as effective drug delivery: A review. Current Nanomaterials, 4: 71-83. https://doi.org/10.2174/2405461504666190527101436.

Shriram, R.G., A. Moin, H.F. Alotaibi, E.-S. Khafagy, A. Al Saqr, A.S. Abu Lila & R.N. Charyulu (2022). Phytosomes as a plausible nano-delivery system for enhanced oral bioavailability and improved hepatoprotective activity of silymarin. Pharmaceuticals, 15: 790. https://doi.org/10.3390/ph15070790.

Singh, A., A. Ray, R. Mishra, P.K. Biswal, R. Yadav & S.K. Ghatuary (2020). Phyto-Phospholipid complexes: Innovative approach to enhance the bioavailability and therapeutic efficacy of herbal extract. Pharmaceutical and Biosciences Journal, Pages 01-09. https://doi.org/10.20510/ukjpb/8/i4/1593521611.

Singh, A.N., B. Mahanti & K. Bera (2021). Novel drug delivery system & it's future: an overview. International Journal of Pharmacy and Engineering, 9: 1070-1088. http://www.abhipublications.org/journal/G_191_I.pdf.

Singh, R., S. Parpani, R. Narke & R. Chavan (2014). Phytosome: Recent advance research for novel drug delivery system. Asian Journal of Pharmaceutical Research and Development, Pages 15-29. http://www.ajprd.com/index.php/journal/article/view/185.

Sivadasan, D., M.H. Sultan, S.S. Alqahtani & S. Javed (2023). Cubosomes in drug delivery—A comprehensive review on its structural components, preparation techniques and therapeutic applications. Biomedicines, 11: 1114. https://doi.org/10.3390/biomedicines11041114.

Supraja, B., & S. Mulangi (2019). An updated review on pharmacosomes, a vesicular drug delivery system. Journal of Drug Delivery and Therapeutics, 9: 393-402. https://doi.org/10.22270/jddt.v9i1-s.2234.

Surini, S., H. Mubarak & D. Ramadon (2018). Cosmetic serum containing grape (*Vitis vinifera* L.) seed extract phytosome: Formulation and in vitro penetration study. Journal of Young Pharmacists, 10: S51.

Tan, Q., S. Liu, X. Chen, M. Wu, H. Wang, H. Yin, D. He, H. Xiong & J. Zhang (2012). Design and evaluation of a novel evodiamine-phospholipid complex for improved oral bioavailability. Aaps Pharmscitech, 13: 534-547. https://link.springer.com/article/10.1208/s12249-012-9772-9.

Telange, D.R., A.T. Patil, A.M. Pethe, H. Fegade, S. Anand & V.S. Dave (2017). Formulation and characterization of an apigenin-phospholipid phytosome (APLC) for improved solubility, in vivo bioavailability, and antioxidant potential. European Journal of Pharmaceutical Sciences, 108: 36-49. https://doi.org/10.1016/j.ejps.2016.12.009.

Telange, D.R., A.T. Patil, A.M. Pethe, A.A. Tatode, S. Anand & V.S. Dave (2016). Kaempferol-phospholipid complex: formulation, and evaluation of improved solubility, in vivo bioavailability, and antioxidant potential of kaempferol. Journal of Excipients and Food Chemicals, 7: 1174. https://fisherpub.sjf.edu/pharmacy_facpub/128/.

Tran, N., B. Pham & L. Le (2020). Bioactive compounds in anti-diabetic plants: From herbal medicine to modern drug discovery. Biology, 9: 252. https://doi.org/10.3390/biology9090252.

Tripathy, S., D.K. Patel, L. Barob & S.K. Naira (2013). A review on phytosomes, their characterization, advancement & potential for transdermal application. Journal of Drug Delivery and Therapeutics, 3: 147-152. https://doi.org/10.22270/jddt.v3i3.508.

Vu, H.T., S.M. Hook, S.D. Siqueira, A. Müllertz, T. Rades & A. Mc Dowell (2018). Are phytosomes a superior nanodelivery system for the antioxidant rutin? International Journal of Pharmaceutics, 548: 82-91.

Wanjiru, J., J. Gathirwa, E. Sauli & H.S. Swai (2022). Formulation, optimization, and evaluation of *moringa oleifera* leaf polyphenol-loaded phytosome delivery system against breast cancer cell lines. Molecules, 27: 4430. https://doi.org/10.3390/molecules27144430.

Xu, K., B. Liu, Y. Ma, J. Du, G. Li, H. Gao, Y. Zhang & Z. Ning (2009). Physicochemical properties and antioxidant activities of luteolin-phospholipid complex. Molecules, 14: 3486-3493. https://doi.org/10.3390/molecules14093486.

Xu, L., D. Xu, Z. Li, Y. Gao & H. Chen (2019). Synthesis and potent cytotoxic activity of a novel diosgenin derivative and its phytosomes against lung cancer cells. Beilstein Journal of Nanotechnology, 10: 1933-1942. https://doi.org/10.3762/bxiv.2019.61.v1.

Yu, F., Y. Li, Q. Chen, Y. He, H. Wang, L. Yang, S. Guo, Z. Meng, J. Cui & M. Xue (2016). Monodisperse microparticles loaded with the self-assembled berberine-phospholipid complex-based phytosomes for improving oral bioavailability and enhancing hypoglycemic efficiency. European Journal of Pharmaceutics and Biopharmaceutics, 103: 136-148. https://doi.org/10.1016/j.ejpb.2016.03.019.

Yu, Z., X. Liu, H. Chen & L. Zhu (2020). Naringenin-loaded dipalmitoylphosphatidylcholine phytosome dry powders for inhaled treatment of acute lung injury. Journal of Aerosol Medicine and Pulmonary Drug Delivery, 33: 194-204. https://doi.org/10.1089/jamp.2019.1569.

Yue, P.-F., W.-J. Zhang, H.-L. Yuan, M. Yang, W.-F. Zhu, P.-L. Cai & X.-H. Xiao (2008). Process optimization, characterization and pharmacokinetic evaluation in rats of ursodeoxycholic acid–phospholipid complex. AAPS Pharm Sci Tech, 9: 322-329. https://link.springer.com/article/10.1208/s12249-008-9040-1.

Zhang, K., M. Zhang, Z. Liu, Y. Zhang, L. Gu, G. Hu, X. Chen & J. Jia (2016). Development of quercetin-phospholipid complex to improve the bioavailability and protection effects against carbon tetrachloride-induced hepatotoxicity in SD rats. Fitoterapia, 113: 102-109. https://doi.org/10.1016/j.fitote.2016.07.008.

Zhu, S., C. Luo, W. Feng, Y. Li, M. Zhu, S. Sun & X. Zhang (2020). Selenium-deposited tripterine phytosomes ameliorate the antiarthritic efficacy of the phytomedicine via a synergistic sensitization. International Journal of Pharmaceutics, 578: 119104. https://doi.org/10.1016/j.ijpharm.2020.119104.