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Progressive Journey of Phytosomes: Preparation, Characterization, Patents, Clinical trials & Commercial products

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ABSTRACT: Phytosomes stand sophisticated herbal preparations that contain the phytoactive ingredients found in extracted from herbs and have the ability towards change the cell membrane's hydrophilic to lipophilic state. They may be produced as pills, creams, gels, suspensions, and other medicinal forms. Many illnesses now have a fantastic treatment alternative in phytosomes. Their therapeutic applicability may be limited by poor bioavailability and selectivity. A potential possibility for the delivery of insoluble phytochemicals has been introduced: nano-vesicles. The most commonly formulated substances are curcumin and silymarin. A variety of human and animal systems, including the cardiovascular, digestion, urination, immunological, muscle-skeletal and integumentary, pulmonary and respiratory systems, have been the subject of more than 100 studies looking at the effects of phytosomes. This list contains the quantity of articles on phytosomes and their biological functions, broken down by the system being studied. The existing method of delivering topically applied bioactive phytochemicals may be drastically altered by phytosome nanotechnology. The main problems are the inadequate penetration through biological barriers and the very low absorption rate (specifically, the skin). Phytosomes which are nanocarriers made up of lipids are essential for enhancing polyphenolic chemicals that come from herbs. A novel, patented method called phytosomes produces lipid-compatible molecular complexes by complexing standardized plant extracts or water-soluble phytoconstituents with phospholipids. This significantly increases absorption and bioavailability by increasing the hydrophilicity of a highly lipophilic drug, the phytosome or herbosome approach makes it ideal for drug administration.

KEYWORDS: Phytosomes; drug delivery system; phyto-phospholipid complex; polyphenols; flavonoids; clinical trial.

1. INTRODUCTION

A phytosomes are a vesicular drug delivery system with phytoconstituents and lipid on both sides. Herbal extracts are more easily absorbed when they are consumed orally or administered topically. Phyto and some other terms refer to things that resemble cells. Phytosomes may readily cross the lipophilic route of the enterohepatic cell membrane. The phospholipids used are phosphatidylcholine (PC), phosphatidylserine, phosphatidylethanolamine, and phosphatidylinositol, but PC is the most commonly used one due to its potential therapeutic benefits for liver diseases like hepatitis, alcoholism, alcoholic steatosis, and drug-induced liver damage [1]. The levels of TNF-induced PDGF, CXCL10, and RANTES were reduced by the ginkgo biloba phytosome as well as the baseline release of PDGF. According to the information gathered, lipoic acid showed a broader and stronger inhibitory action on the release of cytokines and chemokines in relation to the Ginkgo biloba phytosome. In contrast to Ginkgo biloba, which seemed to primarily affect, this research found that lipoic acid significantly inhibited TNF-induced NF-B and p38/MAPK activation [2].

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Phospholipids derived since soy, particularly the lipid-phase compound PC compounds effectively used by Indena to produce lipid-compatibility of flavonoids (PC). Phytosomes and liposomes are structurally distinct from one another [3].

The high lipid miscibility of this hybrid makes it more suitable to combine with the outer cell membrane's lipid phase of the enterocyte phytosomes, a compound designed to boost the uptake and bioavailability of plant extracts and water-soluble phytoconstituents into phospholipids. Phytosomes are herbal medications that have been placed inside vesicles. Effectively absorbing from the lipophilic environment of the cell membrane into a water-loving environment, they may eventually enter the blood circulation. Phyto-phospholipid complexation is one of the best ways to improve how well herbal medicines and nutraceuticals are absorbed and used by the body [4].

The flavonoid and terpenoid parts of these plant preparations may be able to directly bind PC. Phospholipids and bioactive chemicals make up the fundamental formulation of phytosomes. In a nonpolar solvent, phospholipids and aromatic active phytoconstituents are linked to herbal extracts to make micelles. The pharmacokinetic and pharmacological parameters of phytosomes have improved [5].

2. STRUCTURE OF PHYTOSOMES

The active phytoconstituents and the polar head (choline moiety) combine physically and chemically to generate Guggulosomes and phytosomes, which complexes of phyto-phospholipids in their chemical makeup **(Figure 1)**. These complexes entail the anchoring of phospholipid head groups. In complexes that result in the creation of a lipophilic surface, the polar component is encapsulated by fatty acid chains. The substance that makes up a liposome is active, either in a cavity between the membrane's several layers [6]. The substance that makes up phytosomes active is a component of the membrane itself.

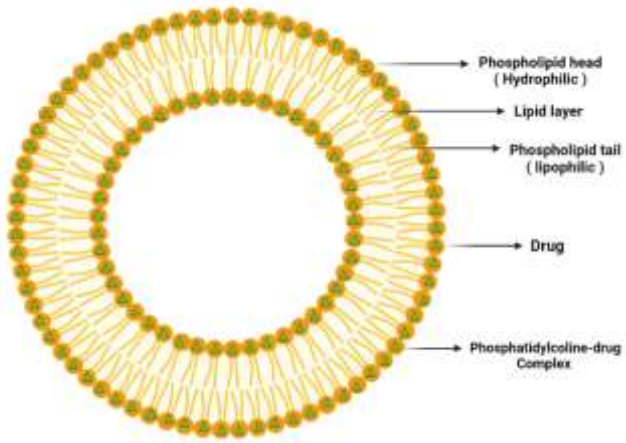

Figure 1. Structure of phytosomes [7].

3. COMPONENTS OF PHYTOSOMES

A phytoconstituents, the role of phospholipids and the stoichiometric ratio in the as well as solvents are the four key components listed in the current literature for the production of phyto-phospholipid complexes. In addition to polyphenols, additional compounds may be used as the active component in phytosomes, such as 20(R)-25-methoxyl-dammarane-3,12,20-triol (25-OCH3-PPD), siramasin, and evodiamine [8]. So, phytosomes are not just polyphenols, and complexes made from them could, in theory, be mixed with any active moiety.

3.1. Plant-Based Ingredients

Researcher-selected phyto-active components extracts from plants are evaluated for their pharmacological action shown in vitro as opposed to their effects in vivo. Most in these chemicals are polyphenols, some of those are seen in polyphenolic components have a preference considering the aqueous phase and are unable to pass via membranes in living things. Others, such by way of rutin and curcumin,

alternatively, there are lipophilic characteristics then are not soluble in fluids in the stomach that are aqueous. Both the solubilization that are lipophilic polyphenols the phase of water as well as cell membrane permeability with hydrophilic polyphenols since the water phase are improved by phyto-phospholipid complexes. Additionally, the creation of complexes may shield polyphenols from photolysis, oxidation, and hydrolysis [9].

3.2. Phospholipids

Phospholipids stand widely distributed inside of a plant, an egg yolk, they are, and classified based on their backbones, specifically sphingomyelins and glycerophospholipids. The primary components of glycerophospholipids are Phosphorylcholine, Phosphorylethanolamine, Phosphorylglycerol, Phosphorylserine, Phosphorylinositol, and Phosphodic Acid (PI). Currently, commercially produced phospholipids may be found on the market. The main phospholipids involved in the production of complexes with a hydrophilic head group, two hydrophobic hydrocarbon chains, and are PS, PE, and PC [10]. Due to its amphipathic character, which allows for mild solubilization in aqueous and lipid solutions media, PC is the most preferred phospholipid among them and is used in the creation of phospholipid complexes. PC is also an important a component of cell membranes helps explain why it works well with living things and doesn't harm them.

3.3. Phyto-Active Constituents and Phospholipids in a Stoichiometric Ratio

Ordinarily, phytoconstituents stand combined using either natural or synthetic phospholipids in a Varying molar ratios of 0.5 to 2.0 to create phytosomes, although a stoichiometric ratio of 1:1 is most often used to create phospholipid complexes. For instance, lipoid S 100 and quercetin were combined in a 1:1 ratio to create quercetin phytosomes. SPC Lipoid® S 100 together with curcumin were combined in a 1:1 molar proportion to create the curcumin phytosomal soft gel and phytosomes. According to the findings, the produced formulations are more stable and include encapsulated phytosomes. In a different investigation, the scientists manufactured diosgenin phytosomes using a 1:1 molar ratio is effective against lung cancer cells the findings indicated higher cytotoxic effects in opposition to human cancer cells, increased diosgenin water solubility.

However, studies have used a range phospholipid and active components in stoichiometric proportions. Different stoichiometric ratios of silymarin phytosomes, such as 1:5, 1:10, and 1:15, were synthesised. According to the authors' findings, the 1:5 stoichiometric ratio produces phytosomes that have the largest drug loading and the best physical characteristics. Carry out a comparison investigation using the following stoichiometric ratios to synthesise phytosomes: 1:1, 1.4:1, 2:1, 2.6:1, and 3:1. The findings indicated that the 3:1 stoichiometric ratio was the most effective. Additionally, chrysin-loaded phytosomes were created to improve muscle cell absorption of glucose. According to the authors' findings, a using a 1:3 molar ratio shown toward be the maximum stable [11]. As a result, 1 to 1 molar ratio is not required aimed at the production interactions of phospholipids. To achieve specific goals such as high drug loading, the phospholipid/active transporter stoichiometry ingredients would be modified for various kinds of pharmaceuticals.

3.4. Solvents

A number have been used in the past used by scientists for the synthesis of phospholipid phytocomplexes. In most cases, aprotic solvents such as ethyl acetate, hydrocarbons, cyclic ethers, halogen derivatives, and methylene chloride have all been used towards synthesise complexes of phytophospholipids. However, owing to their success rate, ethanol and methanol are examples of prototic solvents have taken their place. In research to treat inflammatory disorders, the combination of rutin and phospholipids created using methanol. The authors developed a polymeric matrix patch for a better medication retention period over the skin. Results indicated that the improved preparation exhibits 31.32 and 26.56% of the skin penetration, then the patch's anti-inflammatory impact demonstrated its efficiency in a rat-paw oedema model when compared to standard diclofenac gel. In order to improve the absorption of glucose in muscle cells, developed chrysin-loaded phytosomes. Solvent evaporation technology is used as a way to create phytosomes that are loaded with chrysin [12]. It was phytosomes created through integrating phospholipids from eggs or soy PC.

4. PREPARATION OF METHODS

The unique compound known as a phytosome is made up of lipids and plant extracts. A technique known as phytosomal phospholipid binding was developed to bind the standardised extract of the herb's active components to phospholipids like PC either phosphatidyl ethanolamine or phosphatidyl serine via a polar end. A phospholipid that is either natural or synthetic and 3-2 moles of an herbal extract are combined to form a phytosome. The reaction takes place using an aprotic solvent like the complex is derived from dioxane or acetone may be separated by precipitation combined with non-solvents like Lithium-based hydrocarbons, lyophilization, or by spraying. These two moieties are arranged in a ratio between 0.5 and 2.0 moles during the complicated development of phytosomes. Phospholipids and flavonoids should be used in a 1:1 ratio. **(Figure 2&3)** illustrates the step-by-step method of phytosome preparation. The steps below make up the general technique of making phytosomes [13].

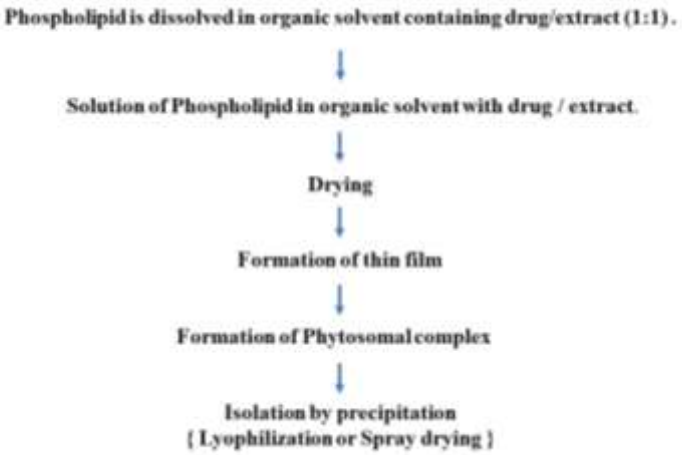

Figure 2. Schematic representation of Phytosomal preparation [14].

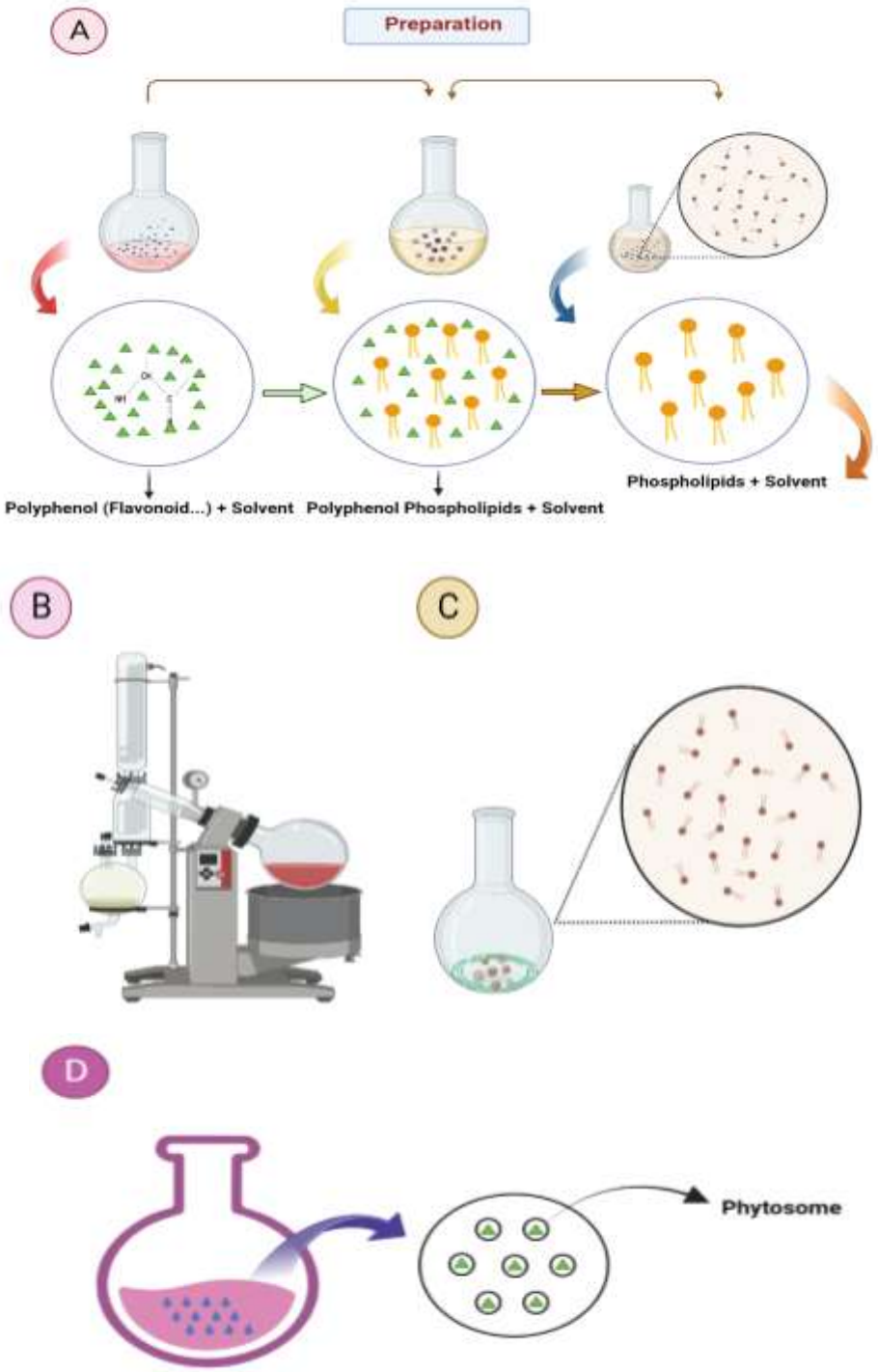

Figure 3. Thin-film hydration technique. **A-**Preparation, **B-** Refluxing and concentration under reduced pressure C**-** drying and thin layer formation **D-**Hydration and size reduction.

4.1. Solvent evaporation technique

A There is a marsupsin-phospholipid complex created by means of a precipitation of liquid antisolvent technique that is mechanically dispersion orientated [15]. The medication and the phospholipids are typically combined in a flask with an appropriate solvent/solvent system when using the solvent evaporation procedure (i.e., tetrahydrofuran and ethanol) [16]. A 1:1 stoichiometric ratio has been deemed the best for forming complexes in the majority of research studies. Until all of the solvents had evaporated, both solutions

were mechanically agitated made the oxymatrine-phospholipid complex using ratios of 1, 4, 2, 6, and 3 between the medication and the phospholipid. The complex was then improved using a composite design approach. The most productive complex was created using a 3:1 ratio at 60°C for three hours. In molar ratios ranging from 1:0.5 to 1:3, [17] created an embelin-PC complex. The best formulation was created with a drug 80 g/l concentration, together with a phospholipid to ratio of 0.9 drugs (w/w) [18]. It was determined that the medication content in the complex was 45.78%, and combined percentage of the final it was formulated 100%. Aprotic solvents, such as methylene chloride, ethyl acetate, dioxane, etc., have greatly supplanted them. Researchers have employed phospholipids from several sources Along with the solvent system in their experiments [19].

4.2. Super-critical fluids being used (SCF)

Supercritical liquids are a powerful tool for particle preparation in large sizes (5–2000 nm). Complexes of purarin and phospholipids were created using 3 different traditional techniques, such as lyophilization, solvent evaporation, and micronized puerarin. Supercritical fluids have been utilised to enhance the solubility characteristics of poorly soluble medication candidates (SEDS). In the GAS method, separate phospholipid and medication solutions were each given a supercritical anti-solvent up prior to the ultimate pressure being applied. The resulting technique produced a 93% yield [20].

4.3. Lyophilization process

Each synthetic and natural phospholipids then phytoconstituents were melted in various solvents, then a mixture that contains phospholipid was additional to another solution including phytoconstituents, which was then stirred until complex formation occurred. The developed complex is separated through lyophilisation. The phospholipids utilised in the process of phytosomes contain acyl group that can be the phosphorylcholine and phosphatidylserine might be the same or distinct and phosphatidylethanolamine are primarily derived from stearic, oleic, palmitic, and linoleic acids [21]. The active principle of phytosomes becomes a structural component.

4.4. Gas anti-solvent method (GAS)

In the gas anti-solvent method, the drug and phospholipid solutions were each individually mixed with a supercritical antisolvent till the desired the ultimate pressure was obtained [22]. After that, the vessel for the reaction was left in place aimed at 3 hours at a constant pressure of 10 mPa and a temperature of 38 °C.

4.5. Enhancing dispersion using supercritical fluids

The phospholipid complex was synthesised using supercritical procedures. The supercritical antisolvent, the liquid solution, and the SEDS process were all infused into the precipitation unit. A 0.1 mm diameter nozzle was used to introduce carbon dioxide gas into the mixture of drugs and puerarin. The final procedure generated a 93% yield complex [23].

4.6. Anti-solvent precipitation technique

Numerous studies in addition to the conventional a precipitate of anti-solvent method, including n-hexane by way of the antisolvent, toward precipitate out the pharmaceutical compound of phospholipids the organic solvent [24]. Research is based on a patented procedure for producing a combination of phytophospholipids with andrographolide employing the anti-solvent is n-hexane, while dichloromethane serves as the reaction media for this product's ultimate precipitation. As a result, subsequently removed by evaporation, and the residue is typically dried in a vacuum [25]. Anhydrous co-solvent lyophilization was used in a more recent study to create a rutin-phospholipid complex methanol was used to dissolve both the medication and the phospholipids, although at separate rates containers. Mechanical stirring was used to combine the two solutions until all of the solvents had evaporated. As opposed to the crystalline rutin, the rutin-phospholipid complex was shown by photomicrography to be in an amorphous form. When the ratio of medicine to phospholipids was 1:3, the results were much better [26].

4.7. Rotary evaporation technique

Thirty millilitres of tetrahydrofuran were used to dissolve the specified amount of plant material and phospholipid in a rotating circular bottom flask. The mixture was then agitated for three hours at a temperature below 40 degrees Celsius. Sample was in a thin film, and assembled, the addition of n-hexane, and the mixture was using a magnetic stirrer, the mixture was continually swirled. In a glass container that is amber in colour, the precipitate was removed and put down at ambient temperature [27].

4.8. Ether-injection technique

In this procedure, an organic solvent is used to dissolve the drug's lipid complex. The development of vesicles is then triggered by the mixture being gently infused into an aqueous agent that has been heated. Focus determines the condition of amphiphiles. At low concentrations, amphiphiles work as monomers, but as the concentration goes up, different structures can form, such as spherical, cylinder, disc, cubic, and hexagonal structures [28].

4.9. Cosolvent

An organic solvent, such as methanol, is used to dissolve the extract and PC. An hour of swirling with a magnetic stirrer was used to complete the mixing [29].

4.10. Salting out

The extract and PC are dissolved in ethanol before being stirred together. The process of precipitation creation involves adding n-hexane to the mixture to create a precipitate phytosome [30].

4.11. Thin layer hydration

Cholesterol was dissolved in dichloromethane, whereas fraction, PC, and were all dissolved in methanol. Once the solvent has entirely vaporised, with a thin dry layer has developed on the bottom of the container, the mixture is gently evaporated at 45°C using a rotary evaporator. The resulting thin film of lipid is then pumped combined with nitrogen gas kept prior to by one night at room temperature receiving hydration treatment. On a rotary evaporator set at 45°C, aquabidest was used to hydrate the film layer. Using sonification and a homogenizer, the technique to calculate particle size was also optimised [31].

4.12. Some specifications

Phospholipids have a stoichiometric ratio of 1:1, which is ideal for constructing a complex. There have been studies using various molar ratios ranging from 0.5:1 to 3:1. used to create the most effective complex. Absolute ethanol has been used as the reaction medium for the majority of contemporary research. Some researchers have use of n-hexane as a medium creating herbosomes [32]. The combined percentage of the resulting formulation was discovered to be 100%, while the complex's drug content was 45.98% [33]. **Table.1** lists recent studies on phytosomes, the methodology used, the solvents used, and the results' value.

Table 1. lists recent research on phytosomes, along with their methodology, solvents, and value.

Different phospholipid complex's	Technique employed	Usage of various solvents	Ref.
Complex of luteolin and phospholipid	The use of Quality by Design for solvent evaporation	Ethanol	[12]
Nanophytosomes that contain rutin	Thin layer hydration method Solvent evaporation method	A mixture of methanol and chloroform(1:4).	[12]
Terminalia Arjuna phytosome combination of methanolic extract (TBE)	Salting out	Methylene chloride and methanol (6:1) n-hexane	[12]

Complex of rosmarinicacid (RA) and phospholipids	Solvent evaporation	Anhydrous ethanol	[12]
Complex of Standardized Centella Extract on Phospholipids	Salting out	Ethanol, n-hexane	[12]
Extract from Phyllanthus emblica phospholipid complex	Solvent evaporation technique	Dichloromethane or methanol as solvent	[12]
Complex of oleanolic acid with phospholipid	Solvent evaporation method 1:1 molar ratio	Anhydrous ethanol	[12]
Complex of echinacoside phospholipids	Solvent evaporation method 1:3 molar ratio	Tetrahydrofuran	[12]
Complexes of silymarin with phospholipid	Solvent evaporation method 1:5	Ethanol	[12]
Complex of epigallocatechin gallate and phospholipid	Solvent evaporation method	Ethanol.	[12]
Extract-phospholipid of pomegranates	Spray drying	Equal volumes of dioxane and methanol,	[12]
Complexation of phospholipids in (W. somnifera) NMITLI118RT	Solvent evaporation method	Ethanol	[34]
Phytosomes Containing Naringenin-Loaded DipalmitoylPC	Solvent evaporation method	Methanol, ethanol, and ethyl acetate	[35]
Phytosome-loaded complex of gingerol soya Lecithin	Anti-solvent precipitation technique	Methanol	[36]
Phytosome Made of Polyphenols from Moringa Oleifera Leaf Tofu PC	Thin-layer hydration method	Dichloromethane, ethanol	[37]
Phytosome with apigenin and phospholipid the Phospholipon® 90H	Solvent evaporation method	1, 4–dioxane, methanol	[38]
Phospholipid vasaka complex	Thin layer hydration technique	Dichloromethane.	[39]
Combination of phospholipid and curcumin	Solvent evaporation method	Dichloromethane	[40]
Complex of soybean PC and mitomycin C	Solvent evaporation method	Distilled water	[41]
Phytosomes of Piper longum	Solvent evaporation method	Aprotic solvent	[42]
Phytosomes based on berberine-phospholipid complex	Solvent evaporation technique	Hot ethanol	[43]
Aloe-vera extract phytosomal gel	Thin-layer hydration method.	Chloroform	[44]

Extract of Euphorbia neriifolia Linn. Phospholipids Complex	Solvent evaporation method	Dichloromethane	[45]

5. PHYTOSOMES' BIOLOGICAL FUNCTIONS

5.1. Evidence of Phytosomes' Function in the Nervous System

5.1.1. The Role of Phytosomes in Neuronal Damage and Cognitive Impairment

In animal models, the bioavailability of phytosomes compared to similar unformulated products has been examined. Following the injection of a specific hydrophosome, discovered a higher concentration of Boswellia acids in Boswellia serrata [46]. Looked into silymarin's capacity to prevent ethanol-induced brain damage in unborn rats. Gamma-glutamyl transpeptidase was one of the antioxidant enzymes with typically higher activity in the phytasome formulation group.

Reduced pentobarbitone-induced sleep duration and reduced effects of chlorpromazine in Wistar rats were observed Curcumin phytosomes from the hippocampus and cerebellum of rats have been shown to reduce neuroinflammation and the number of activated microglia. A second study assessed the antioxidant activity in the rat brain for four weeks following either acute (7 days) or subchronic (14 days) therapy [47].

5.1.2. The Role of Plant Phytosomes in Neurodegenerative Disorders

Dementia develops in older people as a result of neurodegenerative brain malfunction. To enhance the delivery of drugs or active substances with low brain availability, studied the nanoparticle system. Oxidative stress in PC12 cells (a neuron cell line) was reduced by treatment with phytosomes, and the result was better than the unformulated genistein explored the brain transport of the isoflavone genistein by trying several nanotechnological techniques. The phytochemical curcumin phytosome was shown to increase curcumin bioavailability in the hippocampus and frontal lobe after being administered orally to rats for five days (134 mg/kg/die as curcuminoids equivalent).

Curcumin showed up in the frontal lobe of the rat brain 30 minutes after treatment, peaked at 1 hour, and then started to return to normal after 3 hours, proving that the curcumin phytosome can enter the rat brain [48]. The fact that curcumin has anti-amyloid and anti-inflammatory properties, which are mostly used to treat neurodegenerative illnesses like Alzheimer's disease, suggests that future research on medication delivery might benefit from this discovery.

5.1.3. The Role of Phytosomes in Brain Ischemia

The possible benefits of natural substances in the middle cerebral artery occlusion model in rats were examined in two investigations by the same team. A phospholipid molecule containing rutin, a glycoside of the flavonoid quercetin, has been investigated for its bioavailability in an animal model of cerebral ischemia. Rutin was given to Sprague-Dawley rats at a dose of 100 mg/kg, and it was discovered using LC-MS/MS analysis that rutin entered the brain at quantities between 20 and 50 ng/g.

In an animal model of stroke, a rutin-loaded formulation greatly improved functional results. In the second experiment, rats were given a phytosomal complex comprising an ethanolic extract of the roots of Ashwagandha (Withania somnifera) orally (85 mg/kg) one hour before ischemia and six hours after reperfusion. Treatment resulted in a significant reduction in the percentage of cerebral infarction (82.7%) and improved protection against all neurological impairment indicators [34].

5.1.4. Phytosomes' impact on neuropathy

Studied the clinical efficacy of curcumin phytosomes (500 mg), lipoic acid (300 mg), and B vitamins in patients with carpal tunnel syndrome awaiting surgical intervention (3 months, n = 180). Patients who received supplements twice daily before and after surgery for three months had fewer night problems at 40 days and were less likely to have a positive Phalen's test three months later. A comparable formulation based on piperine, curcumin phytosomes, and/or lipoic acid decreased pain (66%) in all combinations in neuropathic

patients after 8 weeks [49]. While lipoic acid alone did not provide statistically significant benefits, supplementation reduced the usage of conventional medication (i.e., dexibuprofen) by 40%.

5.1.5. *The Role of Phytosomes in Neurological Cancer*

One of the most malignant cancers of the central nervous system is glioblastoma investigated the potential of curcumin phytosome intranasal administration to induce GBM remission in the mouse brain. In 50% of the animals, the tumour was in remission; comparable results were also obtained with intraperitoneal injection [50]. Additionally, the medication caused the proteins STAT3 and ARG1 to be suppressed, whereas IL-10 caused STAT1 to be increased.

5.2. The Role of Phytosomes in the Digestive System

5.2.1. The Role of Phtosomes in Pancreatic Cancer

In a prospective Phase II experiment, the synergistic effects of gemcitabine and the curcumin phytosome were examined in advanced pancreatic cancer. A total of 44 patients with locally advanced or metastatic pancreatic cancer were recruited and were given gemcitabine (10 mg/m2/min, infusion over 100 min on days 1, 8, and 15 every 28 days) along with 4 capsules each containing 500 mg of doxorubicin (2000 mg/die). In this trial, the response rate served as the main goal, while progression-free survival, overall survival, quality of life, and tolerability served as the secondary endpoints [51]. The study's findings imply that the use of curcumin phytosomes in combination with gemcitabine may be beneficial for the treatment of pancreatic cancer.

5.2.2. Phytosomes' effectiveness in treating bowel cancer

Athymic nude mice were used to compare in vivo the protective effects of oral silibinin and silybin-phytosome against the development of the human colorectal HT29 xenograft. The silybin-phytosome dose of 100 mg/kg demonstrated effectiveness in lowering tumour weight and volume that was comparable to silibinin 200 mg/kg. Oxaliplatin and curcumin phytosomes were combined to study the efficacy of the treatment in colorectal tumor-bearing animals and oxaliplatin-resistant cell lines in vitro. This combination enhanced the antiproliferative ability of oxaliplatin in vitro when compared to oxaliplatin alone and a control. Additionally, in the HCT116 nude mice xenograft model, a favourable impact was shown, with a decrease in tumour growth, a reduction in the pharmacodynamic markers Ki-67 and Notch-1, and an increase in cleaved caspase-3 [52].

A different study examined the effectiveness of phytosomal curcumin alone or in combination with 5-fluorouracil (5-FU) in an in vivo or in vitro model of colon tumours with colitis. Curcumin significantly enhanced the expression of E-cadherin and suppressed cell proliferation in CT26 cells in a concentration-dependent manner (0–1000 g/mL). When curcumin (25 mg/kg/day) and 5-FU (35 mg/kg/weekly) were combined, the number and size of tumours in mice were reduced. In a mouse xenograft model of colorectal cancer, the same ratio of phytosomal curcumin and 5-FU was used. The results of the research demonstrated inhibition of tumour development, an increase in 5-FU's anticancer activity, and anti-angiogenic actions through regulation of VEGF and VEGFR2 [53].

5.3 The Function of Phytosomes in Diseases of the Respiratory System

5.3.1 The Role of Phytosomes in Asthma and Bronchitis

In healthy participants with mild-to-moderate asthmatic episodes and rhinitis, a pilot study examined the benefits of quercetin phytosomes in addition to standard management (SM). Subjects took one or two QFIT tablets per day (control group) in addition to or instead of SM. After 30 days, the quercetin phytosome + SM group outperformed the control group in terms of avoiding and minimising daytime and nighttime symptoms, maintaining a higher peak expiratory flow, reducing variability, and having a favourable safety profile. A combination of corticosteroids and beta-agonists, the conventional treatment for individuals with moderate or severe persistent asthma, were given to 32 asthmatic volunteers who were recruited in a multicenter research study [54].

Boswellia serrata phytosomes at 500 mg/day were administered randomly to the individuals for 4 weeks, or no further therapy was given. In comparison to patients who only received conventional medication,

participants in the phytosome group required fewer inhalations. Only mild to severe side effects, like not being able to sleep or feeling sick, were reported with phytosome therapy, which was well liked. To increase naringenin's pulmonary bioavailability, and developed a new phytosome. DipalmitoylPC (DPPC), one of the major lipids found in pulmonary surfactant, was successfully employed to administer naringenin. Rats with acute lung damage were used to study the pharmacodynamics of naringenin-loaded DPPC phytosomes for dry powder inhalation (NPDPIs, 10 mg/rat, containing roughly 3 mg naringenin) and to investigate the relevant mechanisms of action. Direct administration of these phytosomes into the lungs of rats showed protection against lung damage [55].

NPDPIs reduced pulmonary edoema by decreasing fluid exudation and significantly decreased the production of cytokines such as COX-2 and ICAM-1, according to the study. Furthermore, the administration of NPDPIs enhanced the ability of naringenin and DPPC to decrease oxidative stress in rats by upregulating SOD activity. A gingerol phytosome complexed with chitosan for the treatment of respiratory disorders has been studied in vitro and in vivo. In vitro testing revealed both the phytosome's prolonged release of gingerol and its anti-inflammatory and antioxidant properties. Antimicrobial activity against the bacterial species that cause respiratory infections was concentration-dependent. In an in vivo pharmacokinetic analysis, the phytosome complex demonstrated an essential sustained-release profile and helped improve gingerol oral absorption. The pharmacodynamic parameters against gram-positive and gram-negative respiratory infection-causing bacteria revealed significant anti-inflammatory action as well as effective sustained antibacterial activity [56].

5.3.2. Role of Phytosomes in Lung Cancer

In a mammary gland tumour cell line (ENU1564) that was injected into the mammary fat of athymic nude mice, curcumin combined with PC was assessed as an anticancer agent. Free curcumin and the phytosome's impact were compared. However, curcumin phytosomes dramatically reduced lung metastasis and the production of MMP-9, a protein linked to tumour invasion and development, including breast cancer both drugs had no effect on tumour volume. In participants taking part in a lung cancer chemoprevention experiment, assessed the biological effects of oral administration of grape seed phytosome. Premalignant and malignant cells of the human lung were studied for phytosomes' effects on prostacyclin and 15-HETE eicosanoid pathways [57]. The findings of this research suggest the use of phytosomes as an anti-neoplastic and chemopreventive drug against lung cancer.

In a different study, oral administration of grape seed phytosomes to athymic nude mice resulted in a down-regulation of the expression of the oncomiRs miR-19a/b and miR-17-92 cluster host gene (MIR17HG) at doses of 200, 300, and 400 mg/kg/day for the group, respectively, containing GSE 56, 84, and 112 mg/kg/day. This was connected to the in vitro grape seed phytosome activity that was seen in lung cancer cells in the same investigation. The maximum dosage of grape seed phytosomes was well tolerated, and at the conclusion of the treatment, bronchial biopsies showed a significant reduction in the Ki-67 labelling index (55%), a significant downgrading of the bronchial histopathology, and a significant downregulation of the expressions of miR-19a, miR-19b, and miR-106b in serum [58].

5.3.3. Potential Effects of Thymoquinone-Loaded Phytosomes Against Human Lung Cancer Cells

Thymoquinone (TQ), a naturally occurring polyphenol, has been linked to a number of pharmacological effects, but its clinical use is limited by its poor bioavailability. Refluxing in conjunction with anti-solvent precipitation led to the development of a unique phytosomal delivery mechanism for the TQ-Phospholipon® 90H complex (TQ-phytosome). Using a three-factor, three-level Box-Behnken architecture, this TQ delivery system was made more efficient. Transmission electron microscopy was used to validate the vesicle size, which was 45.59-1.82 nm for the optimum TQ-phytosome size. An initial burst release was seen within 2 hours, followed by a protracted release, according to the formulation's in vitro release pattern, which suggested a biphasic release pattern. By significantly lowering the IC50 value of TQ-phytosomes (4.31 2.21 M) against the A549 cell line, it was possible to see an impressive increase in dose-dependent cytotoxicity.

Cancer cells accumulated in the G2-M and pre-G1 stages of the cell cycle, which was the distinctive effect of TQ-phytosomes in cell cycle studies. By activating caspase-3, the annexin V staining method also demonstrated enhanced apoptosis induction and cell destruction in TQ-phytosomes. TQ-phytosomes dramatically increased ROS formation in A549 cells when reactive oxygen species (ROS) analysis was

conducted. Finally, using this phytosomal nanocarrier platform, TQ could be delivered with a sustained release profile and greatly enhanced anticancer potency [59].

5.4. The Effectiveness of Phytosomes in Metabolic Syndrome

In 11 individuals with macular edoema brought on by diabetes, a curcumin phytosomal formulation given as tablets improved visual acuity and optical coherence tomography (OCT) retinal thickness. High-density lipoprotein cholesterol (HDL-C or LDL) levels in the subjects hardly changed while they were receiving medication [60]. This combination is especially intriguing for disorders with symptoms of oxidative stress. In a variety of studies, formulations of flavonoids, including quercetin, chrysin, and green tea catechins, have been used to manipulate several MS-related characteristics. The phytosome preparation may have a significant impact on biological activity and bioavailability [61].

5.5. The Role of Phytosomes in Wound Healing

In the treatment of persistent diabetic ulcers in patients with diabetic foot ulcers, a combination of Ginkgo biloba, lipoic acid, and grape seed phytosomes combined with cutting-edge drugs proved helpful 251 in NHDF cells, phytosomes containing Moringa oleifera aqueous leaf extract were shown to be non-toxic up to 3.0 mg/mL. Comparing the formulation at 1 mg/mL to the extract at the same concentration, the formulation had the fastest gap closing time (94.8% after 24 hours). On the other hand, smaller dosages as well as higher doses (1.25 and 1.50 mg/mL) failed to produce results that were statistically significant 252 The effects of combining Calendula officinalis with gold nanoparticle (AuNP) in phytosomal systems were examined in a second in vitro experiment using NHDF cells [62].

For Calendula phytosomes and AuNP-Calendula phytosomes, respectively, the formulations decreased cell monolayer disruptions by 42.2% and 58.7%, respectively (p 0.01). Up to 400 g/mL, the mixture exhibited no harmful effects. In HaCaT cells, a compound of sinigrin and phytosome had favourable effects on wound healing compared to sinigrin alone. In contrast to pure sinigrin, which only reached 71% of the lesion after 42 hours and had little cytotoxicity against cells, the phytosome at 0.14 mg/mL totally healed the wound [63].

5.6. Evidence of the Effectiveness of Phytosomes in Skin Cancer

The potential usefulness of phytosomes in preventing skin cancer was only examined in two research studies. The aforementioned sinigrin-phytosome complex was shown to be cytotoxic to A-375 melanoma cells in the first study. At 0.14 mg/mL, the compound decreased cell viability by over 74%, compared to more than 46% for free sinigrin, yet non-tumorigenic HaCaT cells showed relatively moderate damage. In the second investigation, silymarin's impact on in vitro nanostructured lipid carriers (NLC) was examined [64]. Compared to a commercial formulation of an unidentified phytosome (IC50: 26 g/mL), silymarin-NLC demonstrated a greater suppression of cell viability (IC50: 21 g/mL).

6. DOSAGE FORM OF PHYTOSOMES

There are several oral and topically administered dosing formulations that may be created from phytosome complexes. Several products could be made to get the most out how this technical advancement affects improved bioavailability then formulation manageability.

6.1. Soft gelatin capsules

The best choice for creating phytosome complexes is soft gelatin capsules. It is possible to fill soft gelatin capsules with the phytosome complex after it has been suspended in greasy cars plant-based or partially synthetic oils may stand used for this. Indena advises using granulometry ranging from 100% to create the proper capsules first-pass feasibility experiments must be carried out to identify is the proper vehicle since, Indena is aware of various phytosome combinations that do not exist behave similarly after distributed while driving a car covered in oil and when the suspension is encased in a soft gelatin capsule [65].

6.2. Hard gelatin capsules

Additionally, the complex of phytosomes may stand used to create capsules made with firm gelatin. Although the apparent decreased phytosome density complex tends to bound the total quantity of powder that may stand placed within direct volumetric filling, a capsule direct volumetric filling, a capsule approach (without first compressing) employed for a size 0 capsule, the normal maximum dosage is 300 mg. Using a capsule filling using a piston tamp technique, it stands feasible increasing the quantity with powder that can stand placed inside a capsule, although pre-compression may change the time it takes for the powder to

disintegrate. Indena advises keeping a careful check on the pertinent metrics during product or process advancement. A first-step dry granulation procedure explains the optimal production technique [66].

6.3. Tablets

It's best to use dry granulation method aimed at producing tablets that greater unitary dosages then adequate specialised and biological qualities. As a result of the phytosome complex's limited movement capacity, potential lower, and stickiness apparent a direct compression technique called density should only be used for low unitary doses. To maximise technical properties and produce tablets with appropriate morphology, excipients should be diluted by 60–70% before adding the phytosome complex if a direct compression process is used. While moist granulation is the opposite needs to stand avoided owing The opposite effects of heat then water (during Impact of compaction and drying) on PC complex stable [67].

6.4. TOPİCAL DELİVERY METHODS

Topically apply the phytosome complex the phospholipidic complex must be dispersed across a small area and also the lipidic phase added a previously prepared emulsion developed less at 40 °C), low temperatures in order to successfully incorporate the phytosome complex into an emulsion. The maximum prevalent in topical applications, lipidic preparations cause the phytosome complexes to disintegrate. The phytosome complex should be administered if the final composition has a low lipid component, at a temperature under 40 °C. after being disseminated in the watery process [68].

6.4.1. Phytosomes in Topical Applications

Phytosomes promote the transport of herbal active ingredients to tissues and boost skin absorption and bioavailability. The thick layer of the epidermis's outside known as the SC, is one of the most significant obstacles to the transdermal administration of phytochemicals. Numerous flavonoid compounds attach securely to the phospholipid moieties with a high degree of affinity. In addition to ginseng, grape seed, hawthorn, milk thistle, green tea and just a few examples of herbal extracts that work better when loaded into phytosome formulations different uses of G. Biloba [69].

The introduction of phytosome nanotechnology has the potential to have an influence on the area of medication delivery and might completely transform the way that bioactive phytochemicals are currently delivered topically due to their very low absorption rates and limited penetration through biological barriers (such as the skin), phytochemicals' therapeutic efficacy must be translated from a laboratory context to a clinical one. In order to improve the pharmacokinetic and pharmacodynamic characteristics of polyphenolic chemicals derived from herbs, phytosomes, which are lipid-based nanocarriers, are essential. This makes this nanotechnology a viable tool for the creation of novel topical formulations. Because of their distinct physiochemical properties, the use of this nanosized delivery technology may increase the penetration of phytochemicals through biological barriers, enhancing their bioavailability [70].

Table 2. Interaction of phytochemicals and phospholipids

Phyto-chemical	Category of phytochemical	Variety of Phospholipids	Interaction of Chemicals	Analysis Approach	Ref.
Quercetin	Poly-phenols	PC	With the polar group of the phosphplipid, forms an H-bond.	1H-NMR, 31P-NMR, 13C-NMR	[71]
	Polyphenols	DPPC 1 (PC)	1) Static interactions, (2) creates polar H-bonds with The phosphplipid's polar group, (3) The interaction of hydrophobic molecules with fatty acyl chains.	1H-NMR, , 13C-NMR 31P-NMR	
Lycopene	(Terpenoid) Carotenoids	(PC) DPPC	Involvement of the acyl fatty acid chain in hydrophobic interactions	X-Ray	[72]
Lycopene B-carotene,	(Terpenoid) Carotenoids	(PC) POPC 2	Interaction of the acyl fatty acid chain with the hydrophobic group	X-Ray	[73]
Verbascoside, Tyrosol, Hydroxytyrosol	Poly-phenols	PC	H-bonds are formed with the polar group on the phosphplipid.	1H-NMR, 13C-NMR, 31P-NMR	[74]
Saponin	glycosides Triterpene	PC	Polar group of the phosphplipid forms H-bonds with.	1H-NMR, 13C-NMR, 31P-NMR	[75]
18-_-glycyrrhetinic Acid	Triterpenoids	Soy lecithin	H-bonds form with the phosphplipid's polar group.	Differential Scanning Calorimetry	[76]

POPC: 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine.
DPPC: DipalmitoylPC.

The use of Biloba extract has been reported, and it may be administered topically for its a phenolic phytochemical called quercetin is present in many fruits, vegetables, and extracts of G. biloba that have been complexed with phospholipids. Ginkgo biloba extract complexed with Quercetin-phytosomes phospholipid biloba extract is said to increase peripheral circulation when applied topically, and it is even more effective when combined with phytosome phospholiipid moieties (PC). According to PC-complexed extract of G. biloba showed a minor improvement in the healing potential of secondary memory function [77].

All of these investigations support the formation of chemical connections between phytochemical and phospholipid moieties. Quercetin, which includes hydroxyl groups and a cyclic hydrophobic component, is amphiphilic Lycopene, lycopene and 18 glycyrrhetinic acid all interact when combined with the phospholipid's polar head group by H-bonding Tyrosol, verbascoside, and hydroxytyrosol are examples of chemicals isolated from olive oil fruit [78]. The primary categories of chemical interactions between phospholipids and phytochemicals are shown in **Table 2.** for instance, in the composition of a nanoemulsion, oxymatrine (OXM) crosslinked with PC (OXM-PC) showed greater flux (Jss) and flow resistance (Kp) than free oxymatrine solution (Jss was 253.63 8.62 and 67.87 8.03 g/cm2, respectively).

7. PHYTOSOME SİGNİFİCANCE İN DRUG DELİVERY

In order to increase the absorption of various kinds of phytoconstituents with polyphenolic bases when administered, phytosomes, a new lipid-based delivery system with a structure similar to liposomes, may be employed. The first phytosomes were created in the late 1980s by the Indena firm (Milan, Italy), with the goal

of increasing the substance's bioavailability medications by making them complicated with an example of phospholipids primary phospholipid in phytosomes is PC, with other phospholipids including standardised polyphenolic plant extract also present.

The structure of PC and the phosphate molecule of the bioactive herbal extracts' polyphenolic constituent engage through an H-bond in non-polar solvents to form the lipid-containing phytosomes. The body of phytosomes is composed of polyphenolic phytochemical rings that are water-soluble, such as Terpenoids and flavonoids, which consume a strong chemical empathy for phospholipids' hydrophilic component or choline. The phytoconstituents that are choline-bound yet water-soluble are then incorporated into the tail by the phosphatidyl lipophilic component of phospholipids. Poorly soluble polyphenolic compounds may be improved upon in terms of absorption by being encapsulated into phytosomal delivery systems, which improves their capacity to traverse biological membranes and increases their bioavailability [79].

Due to their ability to migrate across the lipophilic and hydrophilic barriers of the skin, phytosomes' bifunctional character has been shown to increase their pharmacodynamic and pharmacokinetic qualities when administered topically compared to typical herbal chemicals. The future of nanotechnology seems bright technique aimed at the creation of novel preparations because of the potential function that phytosomes in the enhancement polyphenols derived from herbs chemicals a therapeutic method for various ailments. Typically, phospholipids like Phosphatidylserine (PS) and phosphatidylethanolamine (PE) are mixed with the biologically active phytoconstituents in a particular stoichiometric ratio to create phytosomes under predetermined circumstances [80].

After during the mixing process, aprotic solvents such acetone, methylene chloride, ethyl acetate, and dioxane are evaporated continual vacuum to fully remove the complicated ensuring that Phytoconstituents will include absorbed entering the lipids vesicles of phytosomes. The introduction of phytosomes nanotechnology may have an influence on medicine delivery by removing obstacles caused by low the solubility of lipids enhancing how readily available bioactive phytochemicals are including polyphenols, ginkgo, and silybin substances present popular olive oil. A number of products based on phytosomes stand being developed then sold, among them are included **Table 3.**

A water-soluble flavonoid known as silybin is the primary component it has been proven to have the properties of milk thistle, Silybum marianum significant antioxidant and hepatoprotective properties. In a biological membrane rich in lipids, silybin, however, has low solubility and absorption. In compared to free silybin, the milk thistle extract's antioxidant activity was seven times higher to the packaging of the extract as a phytosome delivery system, which improved absorption. Additionally, rats' bioavailability was significantly improved after oral administration of a silybin-phytosome mixture.

Table 3. Marketed Phytosomes containing bioactive phytochemicals.

Formulation of phytosomes	Origin Plant	Complexed phytoconstituents	Phytosomal products	Dose and Dosage form	Mechanism of action	Usage	Ref.
Silybium maranium (Milk Thistle)	Afghanistan.	Silybin, isosilbin, silydianin, and silycristin.	Silybin Phytosome™ (Siliphos®)	120–200 mg of cream, gel, lotion, and emulsion.	Stops the liver's glutathione from being destroyed.	Inflammation, cirrhosis, hepatitis, and hepatoprotective.	[81]
Gingko biloba (Maiden hair tree)	Native to China	Ginkgoic acids from ginkgoflavonglucosides, ginkgolides, and bilobalide, as well as flavonoids from ginkgo, ginkgolides, and bilobalide.	Gingkoselect Phytosome™ Ginkgo select Gingko biloba terpene Phytosome™ Gingko biloba dimeric flavonoids Phytosome™	120 mg; conditioner, shampoo, solution, emulsion. emulson Massage Oils, 20–25mg 1.5% Gel. 100-200 mg	Increases the release of neurotransmitters such as catecholamines and inhibits the enzymes catechol-O-methyl transferase and MAO. The supply of nutrients to the skin is improved by the dilation of capillaries and arterioles. Platelet activating factor cannot bind to its platelet membrane receptor when ginskolides are present. The improvement of lipolysis in fat cells and capillary blood flow is caused by gingko flavonoids' inhibition of the cAMP phosphodies	Anti-aging, anti-asthmatic, anti-amnestic, antidepressant, cardioprotective, calming, and anti-inflammatory properties. Raynaud's illness.	[82]

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					terase enzyme.		
Olea europaea (Olive tree)	Western Asia and northern Africa.	Verbascoside, hydroxytyrosol, and tyrosol.	Oleaselect Phytosome™	-	Reduces the amount of lipid peroxidation and free radicals in the environment. prevents telomerase, protein kinase C, and topoisomerase II from working. 5-Lipoxygenase is selectively inhibited.	Antioxidant, anticancer, anti-inflammatory, and anti-hyperlipidemic.	[83]
Panax ginseng (Ginseng)	China	Ginsenosides	Ginseng Phytosome™	150 mg	The enzymes glutathione peroxidase, glutathione reductase, catalase, and superoxide dismutase work better at fighting free radicals.	Supplements, immunomodulators.	[84]
Camellia sinensis (Tea)	China and Southeast Asia	Epigallocatechin, epigallocatechin-3-O-gallate, catechin, and epigallocatechin.	Green tea Phytosome™	400 mg	. Reduces the activity of the urokinase enzyme, which causes a tumor's growth. enhances the antioxidant defences by boosting the activity of catalase and glutathione peroxidase, among other enzymes.	Nutraceutical, antioxidant, anti-cancer Hepatoprotective, Atherosclerosis, Anticancer, decreases weight, Antidiabetic, Antiinflammatory.	[85]

Vaccinium angustifolium (Blue berry)	northern and Central Europe	Alpha-lipoic acid, tocotrienol complex from anthocyanosides, and bioflavonoids from citrus	VitaBlue Phytosome™	-	-	Memory booster, antioxidant, and vision improvement.	[86]
Curcuma longa (Turmeric)	*South East Asia.*	Curcumin	Curcumin Phytosome™ Curcuvet® (Meriva®)	250 mg and 360 mg	Restrict the production of steroidal hormones, cyclooxygenase, lipoxygenase, cytokines, tissue necrosis factor, and enzymes that break down arachidonic acid. It uncouples oxidative phosphorylation and stabilises the lysosomal membrane.	Osteoarthritis, cancer, and anti-inflammatory	[87]
Vitis vinifera (Grapes)	indigenous to Mediterranean region	Procyanidins, epicatechins, resveratrol, and quercetin are some examples of catechins.	Biovin and leucoselect Phytosome™ Masquilier's Phytosome™	50-100 mg	Increases the endothelium-dependent NO release while shielding endothelial cells from peroxynitrite-induced damage. Oxidative modification is brought on by actions that lower oxidant levels, boost antioxidant levels, and improve LDL resistance.	Antioxidant systemic, nutraceutical, and cardioprotective.	[88]

Echniacea angustifolia (Cone flower)	eastern and central North America	High-molecular-weight polysaccharides and echinacosides (Inulin).	Echniacea Phytosome™	-	Although the exact mechanism of action is unknown, it is thought to activate B and T lymphocytes, hormonal immune defence, and tissue necrosis factor.	Supplements, immunomodulators.	[89]
Panicum miliaceum (Millet)	Northern China.	Amino acids, minerals, unsaturated fatty acids, and vitamins	Millet Phytosome™	Topical preparation	With regard to the skin and cutaneous annexes, the mineral salts, vitamins, and unsaturated fatty acids that are contained in them have a trophic effect (hair and nails).	foods that are anti-stress and healthy for hair, nails, and skin.	[90]
Crateegus oxyacanthoides (Hawthron)	China and Mexico	Hyperin, quercitin.	Hawthron Phytosome™	100 mg	Na+/K+-ATPase in human cardiac muscle tissue is affected via a mechanism independent of cAMP and similar to that of digitalis. blocks the angiotensin-converting enzyme.	Cardioprotective, dietary supplements, and antihypertensive	[91]
Ruscus aculeatus (Butchers' broom)	native to Eurasia.	Ruscogenin, neoruscogenin,	Ruscogenin Phytosome™	Topical preparation	Promote muscular contractions to improve venous circulation through a process involving post-	Sunblock agent, anti-aging, and anti-inflammation.	[86]

					junctional a-adrenergic receptors. inhibit the elastase and hyaluronidase enzymes. .		
Cucurbita pepo (Pumpkin)	America	Carotenoids, steroids, and tocopherols.	Cucurbita Phytosome™ `	Face powder, cream	Prostaglandin production and 5-reductase are inhibited. unable to prevent testosterone from acting as a reductive hormone and from becoming DHT.	Benign prostatic hyperplasia with anti-inflammatory symptoms	[86]
Pinus maritima (Pine)	*south Atlantic Europe*	Procyanidins	Pycnogenol Phytosome™	-	Inhibits the enzymes that lead to inflammation, allergies, and wrinkles.	Anti-inflammatory, anti-aging, and anti-allergenic.	[92]
Syzygium cumini (Jamun)	India	Tannins	Madeglucyl Phytosome™	3 gm/day (Suggested Dose)	Type -2 diabeties.	Anti-inflammatory, anti-hyperglycemic, and antioxidant	[93]
Glycine max (Soy)	East Asia	Genistein and daidzein	Soyselect Phytosome™	400 mg/day (Suggested Dose)	Prevents polymorphonuclear leukocytes from adhering to activated platelets.	Anti-carcinogenic; anti-angiogenic;	[86]
Zanthoxylum bungeanum (Tumburu)	*Southeast Asia*	Hydroxy-a-sanshool	Zanthalene Phytosome™	Emulsion and lotion	Obstructs sodium channels cuts down on the pain-causing impulse's	Anti-reddening and calming	[86]

					transmission.		
Radix puerariae (Kudzu root)	southern and southeastern Asia	Puerarin	Puerarin and phospholipid complex	-	Prevents both tumour necrosis factor-alpha and hypoxia-inducible factor-1 from activating. superoxide dismutase activity is increased, and lipid peroxidation is decreased	Cardiovascular disease, inflammatory disease	[94]
Fraxinus ornus (Flowering ash)	southern Europe and western Asia.	Esculoside (Esculin)	Esculoside Phytosome™	Emulsion	Increases the permeability and fragility of capillaries and maintains the integrity of connective tissue by inhibiting catabolic enzymes like hyaluronidase and collagenase.	Increasing microcirculation, anticellulite, and vasoactivity	[86]
Santalum album (Sandal wood)	Australia	Ximenynic acid, ethyl ximenynate	Ximilene and Ximenoil Phytosome™	Emulsion, lotion, gel	Increases the conversion of arachidonic acid into eicosanoids in the skin. Eicosanoids have a vasokinetic effect and are linked to an increase in microcirculation.	Improves microcirculation	[86]
Ammi visnaga (Khella)	*Europe, Asia, and North Africa*	Visnadine	Visnadex™	Cream, emulsion, lotion, gel	Active antiphosphodiesterase, In order to promote lipolysis in fat cells, lipases are activated	Anticellulite, microcirculation-improving	[86]

					when cAMP concentrations rise.		
Melilotus officinalis (Sweet clover)	Eurasia	Melilotoside, terpenoids, and flavanoids	Lymphaselect™	2 to 60 mg	. Alters the permeability of the blood vessels.	Anti-thrombophlebitis, anti-oedema, and anti-inflammatory	[93]
Citrus aurantium (Bitter orange)	south eastern Asia.	Naringenin.	Naringenin Phytosome™	100mg/kg	Boost catalase, superoxide dismutase, and glutathione peroxidase activities.	Antioxidant	[86]
Centella asiatica (Brahmi)	China, Indonesia, Malaysia, India, Sri Lanka, and so on	Madecassic acid, or asiatic acid.	Centella triterpenoid Phytosome™	60-120 mg	Protection against aberrant increases in capillary permeability and protection against microcirculation.	Skin conditions, ulcer prevention, wound healing, and anti-hair loss medication	[86]
Terminalia serica (Silver cluster leaf)	Africa	Sericoside	Sericoside Phytosome™	3% Gel, cream, emulsion, lotion	Decreased permeability of the capillaries.	Skin remodeling, wound healing, anti-oedema, and anti-inflammatory properties.	[86]

The drug-kinetic profile and improved protection of the brain and arteries of the distribution of ginkgo herbal extract using phytosome nanotechnology were favourable. According to research done on human volunteers, extract of gingko biloba incorporated becoming a delivery mechanism for phytosomes considerably boosted the consumption of its terpenes and flavonoids components. Oleaselect is a widely used product that is produced as a phytosome formulation and is according to the polyphenols in olive oil. When administered by way of a phytosomal preparation as opposed to normal oil, it was revealed to have increased properties that are cardiovascular protective as well as anti-inflammatory, antioxidant, and anti-hyperlipidemic. It was shown that a One Centella Asiatica preparation in the shape of phytosomes improved protection in rats against the harm caused by ischemic-reperfusion hearts and decreased oxidative stress in diabetic patients.

Free radical scavenging, antioxidant activity, and interference with the synthesis of pro-inflammatory cytokines are just a few of the advantages that Greenselect herbal extracts have. The bioactivity of this extract and, therefore, its bioavailability, were both said to be improved by the formulation of Greenselect as phytosomes rutin's phytosomal formulation greatly outperformed rutin's traditional formulation in terms of skin absorption, which in turn increased its anti-rheumatoid arthritis activity. By reestablishing the liver glutathione system, the integration of weakly a soluble form of curcumin phytosome distribution system improved protecting the liver. When compared to the conventional composition, the bioactive curcumin's flavonoids were more easily absorbed by rats when coupled 1,2-dimyristoyl-sn-glycero-3-phosphocholine contains the PC moiety. Other phytoconstituents, like Ruscus aculeatus, Vitis vinifera, Echinacea augustifolia, Cartaegus mexicana , Carteagus species [95], then Echinacea augustifolia species, have been shown to make phytosomes much more effective as medicines.

8. PHYTOSOMES IN CLINICAL TRIALS

In order to do more research on medication safety together with a medicine might exchange dialogue the human body, various formulations made using phytosomes advanced to clinical experiment stage after completing the preclinical studies phase. This is a very important step in getting the FDA's final clearance the first clinical study using a formulation based on phytosomes was carried out in 2007 (NCT00487721, accessed August 28, 2021; ClinicalTrials.gov Identifier: NCT00487721). Silybin, which has been linked to anti-cancer effects was added to phytosomes for usage by patients undergoing prostatectomy for prostate cancer. The early findings showed there is a high oral dosage of phytosome-silibin results in momentary elevations in as well as blood pressure they suggested that this phytosomal composition might one day stand employed as an alternate kind of treatment for therapy for men together along having prostate cancer.

The second investigation which used a silybin-phytosome formulation, was also put through clinical trials (NCT02146118 is the ClinicalTrials.gov identifier, and the access date was August. 28, 2021) formulation using phytosomal, known as Siliphos, stayed studied in mixture treatment through the drug Tarceva erlotinib (erlotinib). They suggested that this mixture might take a synergetic impact Under the care of individuals Having lung cancer that is EGFR mutant, although this research is still being looked at research proceeding the effectiveness filled with extracts of green tea phytosomes against overweightness stayed carried out in 2014. (NCT02542449, accessed August 28, 2021; ClinicalTrials.gov Identifier: NCT02542449). The administered There was a formulation used it to regulate obesity-related weight individuals who had lost weight, and this research is presently in the fourth phase of the clinical trial.

The results indicated that green tea extract phytosomal formulation had a significant impact on maintaining weight in obese people after weight loss® [96]. When synthesised as a phytosome-based formulation, furthermore, grape seed extract tested trendy clinical trials toward see if it was effective against early-stage lung cancer (ClinicalTrials.gov Identification number: NCT04515004, accessed: August 28, 2021). The research findings showed that phytosomal composition caused a >14-day delay in the scheduled operation. When coupled with artichoke leaf dry extract, the bergamot-phytosome formulation has been shown to have anti-hypercholesterolemic action in people with moderate hypercholesterolemia (NCT04697121 is the ClinicalTrials.gov identifier, and the date of access is August 28, 2021). The outcome shows that the management of the developed preparation has a favourable influence relating to lipid and metabolic markers, leading to the achievement of considerable anti-hypercholesterolemic activity.

The most current research, which included a clinical trial, examined using adjuvant advantages of a phytosomal form of quercetin the action of COVID-19 (NCT04578158, ClinicalTrials.gov identifier; accessed August 28, 2021). It remains hypothesised which quercetin phytosome would aid the participants' natural immunity grow and stop the advancement of the COVID-19 condition (i.e., prevent the requirement for hospitalization). The inquiry into the research is still ongoing. The formulations based on phytosomes tested in clinical trials are listed in **Table 4.**

Table 4. List of phytosomal formulations under clinical studies.

Phytosome Formulation	Disorder	Phase and number of clinical trials	Study Result	Reference
Silybin	Prostate cancer	Phase II (NCT00487721)	High blood pressure concentration of silybin	[97]
Silybin	Mutated lung EGFR Adenocarcinoma	Phase II (NCT02146118)	Under examination	[98]
Green tea extract	Obesity	Phase IV (NCT02542449)	Maintaining weight after losing weight	[99]
Grape seeds extract	lung cancer in the early stages	Phase II (NCT04515004)	Delay the procedure by more than 14 days.	[99]
Bergamot	Hypercholesterolemia	Not applicable (NCT04697121)	Antihypercholesterolemic activity	[100]
Quercetin	COVID-19	Phase III (NCT04578158)	Under examination	[101]

9. PHYTOSOMES AND OTHER LIPID-BASED NANOCARRIERS: SIMILARITIES AND DIFFERENCES

The ideal pharmaceutical vehicle for topical dosage forms should enable effective penetration of integrated molecules across skin barriers, preserve to protect the loaded chemicals against deterioration simple towards create, not harmful to the skin, and result in cutaneous Inflammation or sensitivity. The three most popular lipid-based carriers are phytosomes, liposomes, and transferosomes for topical treatments that let water-soluble substances penetrate the skin. Liposomal as well as liposomal skin care items authorised and commercialised since their development, but relatively few transferosomal formulations there have converted via clinical treatments. Researchers examined the similarities and differences between routinely utilised liposomal and phytosomal delivery vehicles [102]. The comparison should be made in light of many nanotechnology-related factors, including the production process, phospholipid content, and lipid vesicle structure.

A thorough grasp of the unique characteristics could raise the calibre of topical goods. Among these are glycosphingolipids, PC, PS, PE, and cholesterol examples of the several lipid types that may being hired to create phytosomes are made of lipid bilayers [103]. The phytosome and the transferosome are primarily composed of phospholipids, an edge activator (10–25%), a trace of ethanol, and water as a carrier. Along with others, these lipids are often utilised to create the delivery systems known as transferosomes and liposomes. A lipid bilayer can be used to hold bioactive chemicals, like herbs, and then put on the skin to help the skin absorb them [104].

Transferosomes' exceptional dermal penetration abilities are due they are very deformable, and capacity towards squeeze through SC then travel as whole vesicles **Table 5** shows the main comparisons and differences between several medication delivery using lipids methods that are often used to put herbal medicines on the skin. Phytosomes are created using procedures that differ from those used to create liposomes and transferosomes. There is no chemical phospholipid molecules' polar moiety and phytoconstituents interact with one another.

Table 5: Different lipid-based drug delivery methods

Properties	Phytosomes	Liposomes	Transferosomes	Ref.
Structure	Lipid bilayer vesicles made up of several phospholipid types that may chemically bind to phytochemicals	Cationic, anionic, and neutral lipids make up the lipid bilayer visecles, which are made up of a greater variety of lipids.	Phospholipids, an edge activator (such as a surfactant or bile salt ranging from 10 to 25%), a little amount of ethanol, and water as a carrier make up lipid bilayer viscles.	[105]
Encapsulation	By forming an H-bond with the phospholipids' polar tip, the bioactive molecules are anchored there.	The lipid bilayer membrane or the aqueous interior of the vesicles both contain the active components.	The aqueous core of the vesicles' active components or the membrane's lipid bilayer contain the active components.	[106]
Preparation	In reality, a 1:1 or 2:1 molecule complex with chemical bonds is formed by the PC and the phytochemicals.	The loaded elements were added to the lipid thin film after the lipid compositions were independently mixed to create the complex, which formed without the formation of any chemical linkages.	The loaded components were introduced to the lipid thin film after the lipid compositions were mixed separately to create the complex without forming any chemical linkages.	[107]
Hydration buffer	Utilize aprotic solvents including ethylacetate, 1,4-dioxane, hexane, acetone, and metyhlenechloride. increased skin absorption	A water or buffer solution was present when it was formed.	When a saline or buffer solution is present to form	[108]
Skin absorption		Decreased skin absorption	Decreased skin absorption and very stable.	
Stability	High stability	reduced stability		[109]

10. CHARACTERİZATİON TECHNİQUES OF PHYTOSOME

The following spectroscopic techniques are used to evaluate how drugs and phytosome interact **(Figure 4).**

S. no.	Character	Technique for determining
1.	Microscopy	➢ Transmission electron microscopy(TEM) ➢ Scanning electron microscopy(SEM)
2.	Size and zeta potential of particles	➢ Photon correlation spectroscopy(PCS) ➢ Dynamic light scattering
3.	% Entrapment	➢ Ultracentrifugation equipment
4.	Transition temperature	➢ Differential scanning calorimetry
5.	Surface tension	➢ High performance liquid chromatography (HPLC)
6.	Spectroscopical evaluations	➢ 1H-NMR ➢ FTIR ➢ 13C-NMR
7.	*In vivo* and *In vivo* evaluation	➢ Examples include tests to determine anti-hepatotoxic activity and skin sensitization studies.

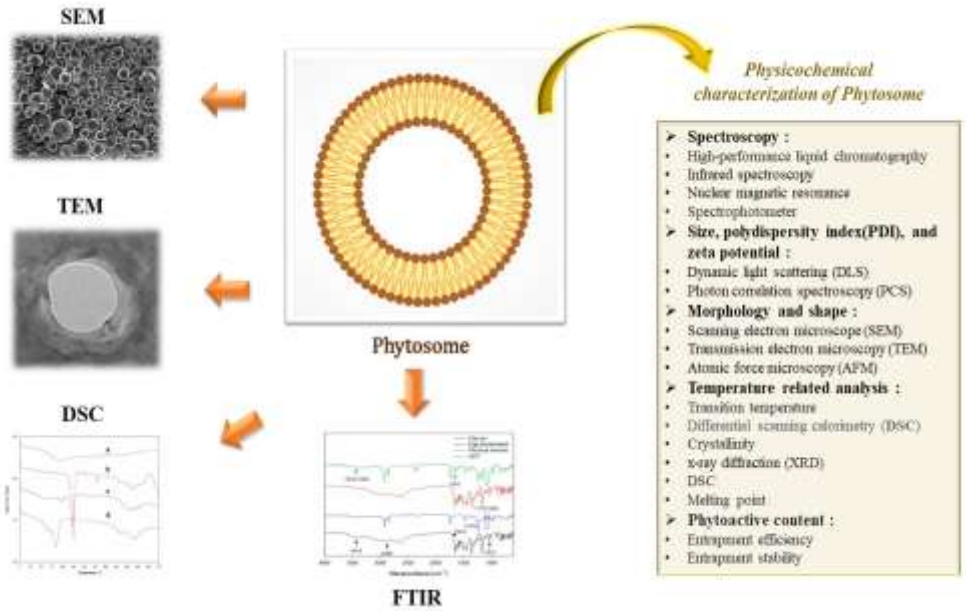


Figure 4. Various characterization parameters of phytosomes.

10.1. Differential scanning calorimetery

Drug-phospholipid complexes, a chemical called PC combination and PC, and medication extract polyphenolic extract stayed all added to an aluminium heated cell and at a rate of 50–250 °C/min between 0 and 400 °C in a nitrogen environment.

10.2. Scanning electron microscopy (SEM)

The particles' size and appearance were assessed using SEM. A dry sample was applied to a brass stub for the electron microscope that had been ion sputter-coated with gold scanning the complex at random speeds of 100.

10.3. Transition electron microscopy (TEM)

Using a 1,000x magnification, TEM remained utilised to describe the phytosomal vesicle's size.

10.4. Entrapment of drugs and loading capability

Centrifuging the substance phytosomal complex at 10,000 90 minutes at rpm and 4°C allowed us towards separate the the phytosome from free drug. Using UV spectroscopy, the amount is a free medicine present may be determined. As shown, it is possible to compute the percentage of drug entrapment.

Formula:

$$\text{Entrapment efficiency (\%)} = \frac{\text{Weight of total drug - weight of free drug}}{\text{Weight of total drug}} \times 100$$

10.5. Fourier transform infrared spectroscopy (FTIR) analysis

FTIR evaluation will be carried out to examine the drug's phospholipids' chemical stability and structural integrity. Using potassium bromide and a pressure of 600 kg/cm2, using phytosomal medication and crushed to create pellets. The range of 4000-400 cm1 will be the scanning range.

10.6. Analysis of sizes and zeta potential

To measure the zeta and particle sizes of phytosomal complexes, the Malvern Zetasizer is used. This zeta and particle size characterization is done using an argon laser.

10.7. Observations made in vivo and in vitro

The results of the in vivo and in vitro testing will rely on the characteristics of the medicine, its main phytoconstituents confined by the phospholipid layer, and the rationale behind the choice of the animal model used for testing [110].

10.8. Spectroscopic evaluation

10.8.1. NMR

A useful technique for understanding molecule structure is NMR spectroscopic analysis. The data may be used to infer the creation of phytosomes by understanding the bonds' quantum mechanical properties and the distribution of electrons in molecules. The example given below will help to illustrate the spectroscopic assessment.

10.8.2. H-NMR

Studies on the (+)-catechin's NMR spectra and the complex it forms in stoichiometry with distearoyl PC have been done. Without any summing of the unique signals from the different molecules, the signal from 1H-NMR coming derived from the atoms a part of the complex's synthesis exhibits a significant shift in nonpolar liquids. To ensure that the flavonoids' protons cannot be released, the signals from these protons must be

strengthened. When it comes to phospholipids, all of the signals expand as opposed to the singlet that the a transformation in choline's N-(CH3)3 upward after the sample has warmed to 60 degrees, shift, several additional wide bands start to show up. These new broad bands mostly correlate to the flavonoid moiety's resonance.

10.8.3. 13C-NMR

All of the flavonoid carbons are visibly absent spectra of 13C-NMR data of (+)-catechin then its stoichiometric combination particularly when reported in combination with distearoylPC C6D6 at ambient temperature. The indicators for the choline and glycerol parts and the lipid (between 60 and 80 ppm), some of them are expanded. displaced, but the majority and resonances for the fatty acid chains maintain their original crisp line form. Around 60, all of an indication from the flavonoid ligands come back, though they continue to quite spread out then overlap in some places.

10.9. In-vivo evaluation

The choice of experimental examples of both in vivo and in vitro testing according to the anticipated therapeutic action of the plant ingredient in phytosome. For instance, the antioxidant, which neutralises free radicals' capacity of phytosomes may be used to evaluate antihepatotoxic efficacy. Animals were used in the in vivo anti-hepatotoxic investigations, which looked at how phytosomes affected alcohol-or paracetamol-induced liver damage [111].

Table 6. Various recent Phytosomal patents

S.No.	Title	Innovation /Novelty	Patent No. (Year of Grant)	References
1.	Curcumin-containing phospholipid complex improved bioavailability	Curcumin that has been combined with phospholipids releases more parent agent into the bloodstream than curcumin that has not been complexed.	WO2009/101551(2009)	[112]
2.	Phospholipid complexes with increased bioavailability that are extracted from olive fruits or leaves.	Phospholipid complexes are used to increase the bioavailability of oil-rich fruit and leaf extracts.	EP1844785(2007)	[113]
3.	Ginkgo biloba derivative-based medicines for the management of allergic and atopic rhinitis.	Ginkgo biloba fraction compositions for treating allergy and inflammatory diseases.	EP1813280(2007)	[114]
4.	Using thymosin -4, treat skin conditions and heal wounds.	The preparation created to promote wound healing contains thymosin -4.	US/2007/0015698/(2007)	[115]
5.	Compositions that may be used orally to treat cellulite.	Pharmaceutical formulation for use in oral and cosmetic products that also includes vitis vinifera extracts, flavonoids from Ginkgo biloba, and triterpenes from Centella asiatica, either free or complexed with phospholipids.	US7691422(2007)	[116]

6.	sorbityl furfural fatty acid monoesters and mixtures for cosmetic and medical applications.	For particular antihydroxyl radical action, sorbityl furfural's chosen fatty acid monoesters and lipophilic agents were used.	EP1690862(2006)	[117]
7.	Skin care products with cosmetic and medical components to repair photodamaged or ageing skin.	The topically applied cosmetic or dermatological preparation that contains at least one ingredient that stimulates collagen production for anti-wrinkle therapy.	EP1640041(2006)	[118]
8.	Formulation of soluble isoflavones	Isoflavone mixtures improved the formulation's colour, solubility, texture, taste, and other attributes.	WO/2004/045541(2005)	[119]
9.	A plant-based antioxidant therapy for circulation and obesity issues	Phlebitis, haemorrhoids, arteriosclerosis, varicose veins, and high blood pressure may all be treated using a formulation made with plant extracts that have anti-oxidant action.	EP1214084(2004)	[120]
10.	Using *vitis vinifera* extracts as an anti-atherosclerotic drug, phospholipid complexes are made.	Phospholipid complexes made from *vitis vinifera* extract are used to cure and prevent atherosclerosis.	US6297218(2001)	[121]
11.	Complexes of bilobalide phospholipids, as well as the uses for them and products that include them	In addition to their synthesis and use in inflammatory situations and for the therapy of neuritic processes, complexes with synthetic or natural phospholipids and bilobalide—a sesquiterpene found in the leaves of the Ginkgo biloba plant—are disclosed. The drug is suitable for parenteral and topical administration since it has a better bioavailability than bilobalide.	EP0441279(1991)	[122]
12.	Neolignane derivative complexes with phospholipids, their application, and preparations for drugs and cosmetics that include them	Complexes of lipophilic plant extracts and a few neolignanes isolated from those extracts demonstrated antibacterial, antimycotic, and antiradical activities, making them a new active principle for the creation of cosmetics and medications as well as an effective preservative in cosmetic preparations.	EP 0464297 (1990)	[123,124]
13.	Pharmaceutical and cosmetic preparations using sponin-phospholipid complexes	Saponins complexes have a higher bioavailability. containing natural phospholipids that are ideal for use in cosmetic, medicinal, and dermatological applications.	EP 0283713 (1988)	[125]

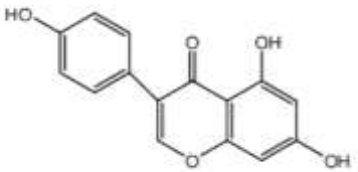
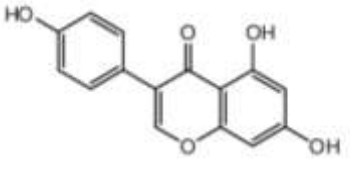
14.	The production of flavanolignan-phospholipid complexes and related medicinal compounds	This invention involves the use of unconventional techniques to produce lipophilic complexes of silidianin, silybin, and silicrist. The resulting complex demonstrated greater plasma levels after having a stronger gastrointestinal absorption as compared to individual flavanolignans. The chemical may be used in the treatment of both acute and long-term liver disorders as a result of its increased pharmacokinetic action.	EP0209038 (1988)	[126]
15.	Pharmaceutical and cosmetic preparations including complex bioflavonoid-phospholipid mixtures, their manufacture and application Isolating them	Comparing complex molecules of flavonoids with phospholipids to free flavonoids, the authors found that the latter had higher lipophilia, enhanced bioavailability, and therapeutic effects.	EP 0275005 (1983)	[127]

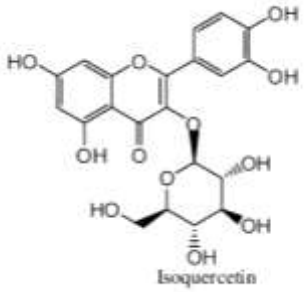
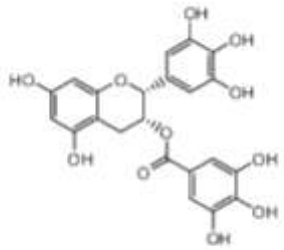
Table 7. Phytosomal products that are offered for sale.

S. No	Brand name	Main constituents	Source	Quantity	Usage
1.	Phytosomes Centella	Triterpine	*Centella asiatica*	-	Trophodermic Cicatrizing.
2.	Phytosomes Ginselect	Ginsenosides	*Gingko biloba*	120 milligram	Adaptogenic
3.	Phytosomes Greenselect	Polyphenols	*Camellia sinensis*	-	Activity that scavenges free radicals
4.	Phytosomes Leucoselect	Polyphenols	*Vitis vinifera*	300 milligram	Antioxidant
5.	Phytosomes Meriva	Curcuminoids	*Curcuma longa*	200-300 milligram	Decreasing inflammation
6.	Phytosomes Silymarin	Silymarin	*Silybum marianum*	-	Antihepatotoxic
7.	Phytosomes Oleaselect TM	Polyphenols of olive oil	*Olea europaea*	-	inflammatory-blocking and antioxidant
8.	Phytosomes Crataegus	Vitexin-2′-O-rhamonoside	*Crataegus Mexicana*	-	Antioxidant
9.	Phytosomes Visnadine	Visnadine	*Ammi visnaga*	-	Improves circulation

10.	Phytosomes Bilberry	Triterpine	*Vaccinium myritillus*	-	Effective antioxidant
11.	Phytosomes Ruscogenin	Steroid saponin	*Ruscus aculeatus*	-	Decreasing inflammation
12.	Phytosomes PA2	Proanthocynidin	*Horse chestnut bark*	-	UV and anti-wrinkle protection
13.	Phytosomes Zanthalene	Zanthalene	*Zanthoxylum bungeanum*	-	Calms and reduces itching
14.	Phytosomes Lymphaselect	Triterpenes	*Melilotus officinalis*	-	Shown in insomnia
15.	Phytosomes Sabalselect	Fatty acid, sterols	*Serenoa repens*	-	Hyperplasia of the prostate in Bening
16.	Phytosomes Sericoside	Sericosides	*Terminalia sericea*	-	Skin enhancer
17.	Phytosomes Echinacea	Echinacosides	*Echinacea angustifolia*	-	Vaccines, nutritional supplements

Table 8. Different flavonoids used in phytosomal preparations.

S.NO	Flavonoid/main components	Herbal name	Assembly
1.	Genistein	Soy tea	 Genistein
2.	Naringenin	Orange	 Naringenin

3.	Isoquercetin	Onion buckwheat hyptis fasciculate	 Isoquercetin
4.	EGCG	Green tea	 EGCG

11. THE NEWEST VESICULAR DRUG DELIVERY SYSTEM

The goal of fresh vesicular medication delivery methods is towards bring the active ingredient to the site of action while delivering the medication at a pace dictated by the body's requirements throughout the treatment time. To accomplish targeted and regulated medication delivery, several cutting-edge vesicular drug delivery systems have been developed, including different administration methods. Targeted medication Deliveries are a way of getting the beneficial substance into the tissues that increases healing effectiveness then lowers adverse effects. When a medicine is targeted, it is given to a particular organ, receptor, or other area of the body **Table 9** [128] gives an overview of a few new and innovative ways to deliver drugs through vesicles.

Table 9. Applications of various vesicular systems.

S.No	Vesicular system	Description	Application
1.	Aquasomes	Ceramic diamond makes up the noncrystalline calcium phosphate core of the particle, which is encased in a polyhydroxyl oligomeric layer.	Targeted specificity, molecular protection.
2.	Aracheosomes	Archeae glycerolipid-based vesicles with strong adjuvant action.	A weak adjuvant activity.
3.	Colloidosomes	They are also hollow, elastic shells with precisely controllable permeability that are produced when colloidal particles self-assemble at the interface of emulsion droplets.	Drug targeting.
4.	Cryptosomes	Surface coat of a lipid vesicle made of PC and an appropriate polyoxyethylene phosphatidyl ethanolamine derivative.	Drug delivery via ligands
5.	Cubosomes	A lipid layer that has been bent into a periodic minimum surface with zero average curvature	Drug targeting.

		separates two independent, continuous, but non-intersecting hydrophyllic areas in bi-continuous cubic phases.	
6.	Discosomes	non-ionic surfactants in combination with niosomes.	Targeting of drugs by ligands.
7.	Emulsosomes	The polar group and lipid assembly made up nanoscale lipid particles.	Poorly water-soluble medication distribution through the parenteral route.
8.	Enzymosomes	On the liposome surface, the enzyme was covalently immobilised.	delivery to a cancer cell with specificity.
9.	Erythrosomes	Liposomal system that uses the cytoskeletons of chemically cross-linked human erythrocytes to coat a lipid bilayer.	Using macromolecular medicines as targets.
10.	Genosomes	Genomes: A synthetic macromolecular system for functional genes transfer.	targeted gene transfer inside cells.
11.	Hemosomes	Immobilizing haemoglobin using polymerizable phospholipids allows one to create liposomes that contain haemoglobin.	large-scale oxygen transport system.
12.	Photosomes	As a result of photo-triggered charges in the membrane permeability properties, photolyase contained in liposomes releases its contents.	Photodynamic treatment
13.	Protostomes	enzyme complexes having catalytic activity that are high in molecular weight.	superior turnover of the catalytic activity compared to enzymes not linked.
14.	Ufasomes	Vesicles made of long-chain fatty acids were produced by mechanically agitating the evaporated film while it was in the presence of a buffer solution.	target medication delivery using ligands.
15.	Vesosomes	Vesosomes Vesosomes are made of nested bilayers that surround an Unilamellar vesicles are found in the aqueous core.	The internal serum content is better protected by vesosomes with many compartments.
16.	Virosomes	Viral glycoprotein-infused liposomes incorporated based on the liposomal bilayer fats made from retroviruses.	adjuvant used in immunology

12. APPLICATIONS

Over the last century, research in phytopharmacological sciences has uncovered information on the chemical make-up, biological functions, and conducive to health properties of plant-based product [129] water-soluble plant components such as the absorption of flavonoids, terpenoids and tannins is low. Phospholipids are the vitamins and minerals that are most beneficial for improving absorption numerous uses of phytosomes are shown in **(Figure 5).**

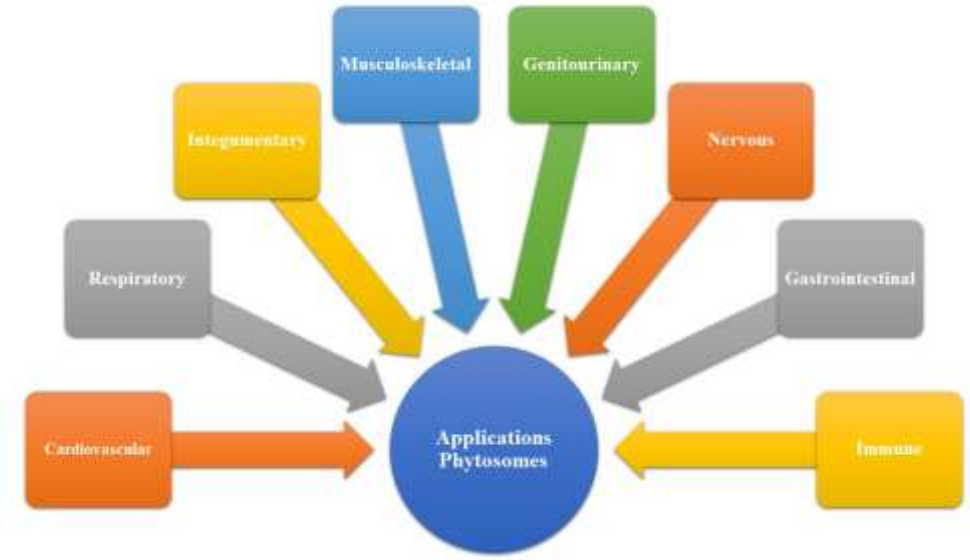


Figure 5. Phytosome applications.

12.1. Silymarin Phytosomes

Silybum marianum, often known as has the best antioxidants that preserve the liver, is the subject of majority of phytosomal research. The Silymarin phytosome was created by investigated the pharmacokinetics in rats. Due to a striking the lipophilic has improved characteristics of silybinphospholipid advanced biological system that is complicated action with silybin, Rats have much higher bioavailability of silybin than raised following complicated medication taken orally in the tests. Physomes of silymarin have stronger anti-hepatotoxic action compared to silymarin alone and can protect the young broiler chickens from detrimental ramifications for aflatoxin B1 [130].

12.2. Curcumin Phytosomes

In two distinct experiments, phytosomes containing the flavonoids naringenin and curcumin, which come from the grapefruit, Vitis vinifera. The complex's antioxidant activity was noticeably greater than that of pure curcumin at every tested dosage level. In the second trial, isozyme of naringenin generated stronger a higher level of antioxidant activity compared to the free compound longer action's time frame, perhaps because the molecule was not being removed from the body as quickly [131]. Curcumin is a safe antioxidant and anti-inflammatory compound with a wide range of pharmacological actions that have been shown in clinical trials to be effective against a wide range of disorders. It has been suggested that one barrier to obtaining the full therapeutic effect from curcumin administration is its limited oral bioavailability.

Here, we evaluated some of the potential strategies that have been tested to enhance the pharmacokinetic profile of curcumin, with a focus on the phytosomal delivery method. A potential method for increasing curcumin's oral bioavailability is phytosome technology, which may also increase the drug's pharmacokinetic characteristics when taken orally. Numerous studies have shown the effectiveness and safety of phytosomal curcumin in the treatment of chronic illnesses. Notably, clinical evidence suggests that phytosomal curcumin may benefit people with osteoarthritis, solid tumors, uveitis, diabetic micro-angiopathy and retinopathy, and benign prostatic hyperplasia.

More research is required to compare the therapeutic efficacy of phytosomal curcumin to other optimised curcumin formulations and unformulated curcumin. The effectiveness of phytosomal curcumin in treating other disorders that are known to respond to curcumin treatment is also not supported by sufficient data. Last but not least, it is advised to do cost-effectiveness studies, particularly in cases where curcumin's benefits [132].

12.3. Quercetin-phospholipid Phytosomal complex

In rat liver damage caused by carbon tetrachloride [133], produced a quercetin phospholipid phytosome complex produced by a straightforward then repeatable approach. They similarly demonstrated because of the formulation displayed superior beneficial effectiveness to the substance.

12.4. Phytosomes of grape seed

The oligomeric polyphenols **(Figure 6)** (proanthocyanidins found in grapes procyanidine from extract from grape seeds; Vitis vinifera) in grape seed phytosomes are complex with phospholipids and have different molecular sizes [134]. They increase capability for all antioxidants, activation of physiological plasma defences, and defence against cardiac damage brought on by ischemia and reperfusion.

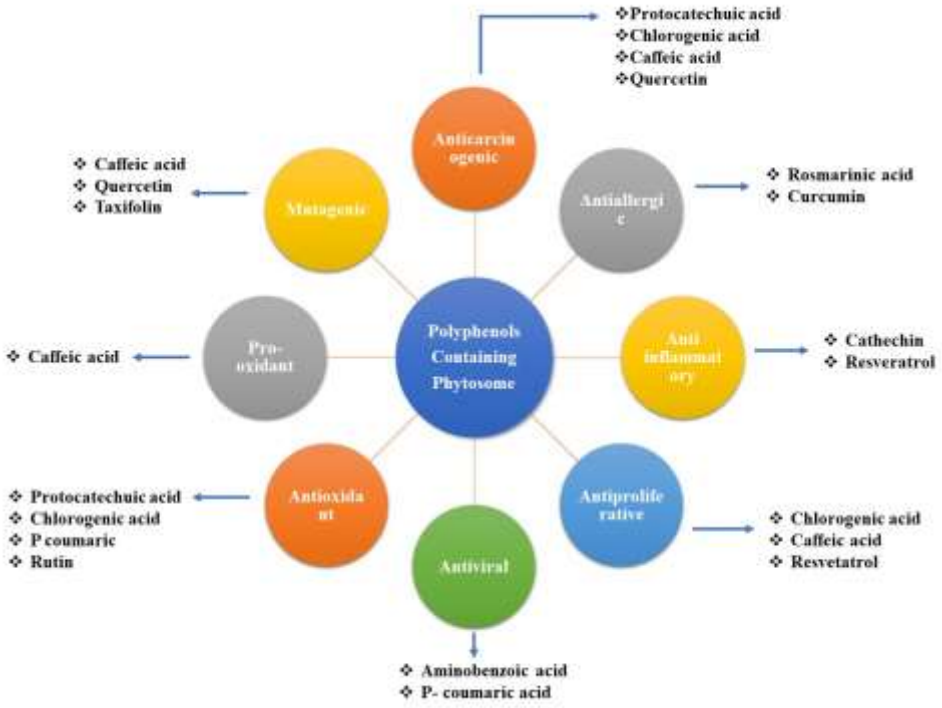


Figure 6. Various polyphenols used in phytosomal formulations.

12.5. Phytosomes of Gingko biloba leaves

Research indicates that ginkgo phytosomes (is formed of standardised Ginkgo biloba leaf extract) fared better than the usual standardised herbal extract (GBE ; 24% of the glycoside of ginkgo flavones and 6% of terpene lactones). Phytosomes are composed of a standardised extract from leaves of the Ginkgo biloba. Phytosomes greater than the usual standardised GBE, which contains 6% terpene lactones and 24% ginkgo flavone glycoside, is a plant extract.

They have been shown to relieve symptoms in people with peripheral vascular diseases by 30–60% more than conventional, standardized GBE [135]. At the greatest peak, the bronchospastic inhibition was quantified and reported as deviations from the baseline values.

12.6. Phytosomes of green tea

The primary component that distinguishes green tea leaves (Theasinensis) is an antioxidant called epigallocatechin 3-O-gallate molecule. These substances stand effective the modulators of number procedure of biochemical connected towards the breakdown in of homeostasis serious long-term degenerative illnesses, including cardiovascular disease and cancer. Additionally, a cup of green tea offers U's a variety of advantageous properties, including antioxidant, anticarcinogenic, and antimutagenic benefits.

In research on the oral absorption of phytosomal preparations and non-complexed green tea extract in healthy human volunteers, when a comparison between phytosomal and non-phytosomal flavonoids was made throughout the course of the study's six-hour duration, that plasma content was more than quadrupled in terms of total flavonoids (Total Radical Trapping Antioxidant Parameter) [136].

13. RECENT DEVELOPMENTS

Cancer treatment uses phospholipid-complex technology for both active and passive targeting. In order to target HeLa cells, created surface-functionalized phytosomes of mitomycin C with folate-PEG. These phytosomes have shown superior effectiveness in both in vitro and in vivo showed that luteolin phytosomes might make MDA-MB breast cancer cells more sensitive to the medication doxorubicin, enabling passive pharmacological targeting of these cells using a solvent-evaporation technique, created a new drug-phospholipid complex for 20(S)-protopanaxadiol (PPD) that was enhanced with micelles.

The researchers discovered that 20 (S)-protopanaxadiol has a 64-fold increase in water solubility. To target the hepatocellular carcinoma (HCC) cell line, co-delivered innovative pegylated nano-liposomal herbal medicines of silibinin and glycyrrhizic acid (nano-phytosomes) (HepG2). According to an in-vitro study, silibinin and glycyrrhizic acid were combined in nano-liposomes, which increased silibinin's biological activity and stability and combined their therapeutic effects.
By combining hyaluronic acid (HA) hydrogel and phospholipid using the solvent evaporation preparation method, created a novel phytosomal technology for the potential ocular delivery of L-carnosine. With this technology, the rheological properties, spreading ability, drug permeation over time, and tolerability all got better.

In-vitro skin permeation of sinigrin from its phytosome complex was established by Mazumder et al. The in vitro research showed that sinigrin was released from the phytosome complex in a regulated and sustained manner. Therapeutic Uses of Phytosome Formulations, **Table.10** Based on what was found, it looked like this sinigrin-phytosome complex could be used to get sinigrin to the skin in the best way possible. By using the reverse-phase evaporation method, able to encapsulate the silybin-phospholipid complex into a liposome, creating a supramolecular aggregate they named Phyto-Liposomes. They then demonstrated their ability to internalise in human hepatoma Huh7.5 cells and showed 300 times more potent pharmacological activity.

Based on the phospholipid-complex method, Amelia et al. created a self-nano emulsifying drug delivery system (SNEDDS). Ellagic acid EA phospholipid complex (EAPL) was initially created using an anti-solvent technique. Later, SNEDDS were created by analysing the EAPL's solubility in various oils, surfactants, and co-surfactants. These results showed powerful ex vivo permeation and in vitro drug release, and they served as a promising method for the creation of other medications or phytoconstituents with low bioavailability [12].

Table 10. Therapeutic Uses of Phytosome Formulations

Sr No.	Trade/Common Name	Company Name	Phytoconstituents Complex	Biological Properties	References
1	Siliphos	Indena	Silybin of silybum marianum	Hepatoprotective and Aanioxidant	[137]
2	Ginseng Phytosome	Natural Factors	Ginsenosides of Panax ginseng	Immunomodulator	[138]
3	Ginkgoselect Phytosome	Herbal Factors	Flavonoids of Ginkgo biloba	Anti-aging and Brain vascular lining	[95]

4	Hawthorn Phytosome	Indena	Flavonoids of Crataegus species	Anti-hypertensive and cardioprotective	[139]

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Conflict of interest statement: The authors declared no conflict of interest.

				Nutraceuticals	
8	Quercefit Phytosome	Indena	Quercetin	Sport nutrition, allergy seasons' discomforts control, anti-oxidant activity	[54]
9	Ubiqsome Phytosome	Indena	CoQ10	Essential endogenous cofactor for the electron transport chain in the mitochondria, antioxidant activity	[143]
10	Casperome Phyosome	Indena	Boawellia serrata Roxb. Ex Colebr Resin	Healthy inflammatory response , Joint health, Gut health	[144]
11	Curcumin Phytosome	Indena	Curcuma longa L. Rhizome	Joint health, Healthy inflammatory response , Soothing	[145]
12	Ginseng Phytosome	Indena	Panax ginseng	Nutraceutical, Immunomodulatory	[96]
13	Centevita	Indena	Asiatic acid , madecassic acid from Centella asiatica	For skin disorders,antiulcer, wound healing ,hair falling	[146]
14	Xanthones Phytosome	-	Swertia alternifolia	Anti-oxidant	[147]
15	Visnadex Phytosome	Indena	Visnadin from Amni visnaga	Improve microcirculation	[148]

CONCLUSION

Phospholipids exhibit affinity for active components via hydrogen bond interactions. The four most popular vesicular drug delivery systems are ethosomes, niosomes, liposomes, and phytosomes denaturation and bioavailability in herbal products are perennially major concerns. Vesicles are prospective cellular delivery vehicles for a number of advantageous phytochemicals. The most effective and innovative methods to use herbs medications in order to deal with these problems are liposomes then phytosomes. Bioactive polyphenolic phytocompounds may more easily overcome biological barriers due to phytosomes and nanoengineered drug delivery vehicles. Although they differ in terms of vesicular structure, phytochemicals and liposomes have the same stability and skin penetration characteristics. In the future, it may be possible to combine phytosomes and drugs in a single nanovesicle to achieve synergistic effects.

LIST OF ABBREVIATIONS

DPPC - Dipalmitoylphosphatidylcholine.
NMR - Nuclear Magnetic Resonance.
GBE - Ginkgo biloba extract.

PC – Phosphatidylcholine
SPC – Soya phosphatidylcholine

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