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Phytosome as an Innovative Carrier for the Delivery of Phytochemicals: A Comprehensive Review

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Abstract

Plant phytoconstituents with few adverse effects make phytomedicine a promising treatment option. Low bioavailability owing to large molecular size, poor lipid solubility, and bioactive component instability hinder its effectiveness. Different methods have been used to create phytochemical carrier systems with increased bioavailability. Most recently, phytosomes have become attractive lipid-based transporters for plant-based medicines and nutraceuticals. A new medicine delivery method called phytosome encapsulates bioactive ingredients in phospholipid molecules, mostly phosphatidylcholine. Phytosomes as phyto-phospholipid complexes improve target medication delivery, bioavailability, stability, pharmacological activity, and bioactive molecule protection against chemical and physical degradation. Phytosomes are widely used and accepted by science due to their efficiency and ease of manufacture. This review covers phytosome technology, its structural components, formulation methods, optimization, characterisation, and pros and cons. Recent research and phytosome-based commercial items are also discussed. In conclusion, phytosome technology is a boon for poorly bioavailable plant extracts and phytochemicals with proven processing and testing methods.

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

Introduction

Phytotherapy based on medicinal plants is an essential aspect of the healthcare system due to its safety, effectiveness, cheap cost, availability, and few or no adverse effects (Jahangir et al., 2020; Mishra, 2022). From ancient times, phytomedicines have helped humans heal incurable ailments and are used worldwide. Due to their therapeutic effects and improved patient compliance, phytomedicines have garnered global interest in recent years (Dongare et al., 2021). Plant-derived bioactive chemicals such phenolic compounds, lignans, alkaloids, and others have several therapeutic effects, including antibacterial, anti-allergic, antioxidant, anticancer, anti-diabetic, and anti-inflammatory capabilities (Tran et al., 2020). Traditional herbal drug dosage forms have poor absorption, decreased biological membrane penetration, and reduced bioavailability owing to high molecular size and lipophilicity, limiting their use (Singh et al., 2020).

Normal dose forms can't manage medication distribution to the target place either. The distribution of medication in non-target sites may need a therapeutic drug dosage that exceeds the target site's needs, causing major side effects (Singh et al., 2021).

Systematic inclusion of plant-based medications into correct dosage forms may boost their efficacy (Dongare et al., 2021). Thus, nano-carrier-based drug delivery must be studied to

overcome traditional dosage and limited bioavailability for improved effectiveness, medication targeting, and patient compliance (Shirsath and Goswami, 2019).

New medication delivery methods

Drug delivery systems provide therapeutic compounds to body targets (Sivadasan et al., 2023). Novel drug delivery systems (NDDSs) for herbal extracts and bioactive chemicals are developing (Singh et al., 2014). Novel phytoconstituent-encapsulated drug delivery methods have advanced greatly in recent decades (Rahman et al., 2020). Novel medication delivery system reduces traditional restrictions. This method improves herbal medicine and phytoconstituent solubility, bioavailability, and stability (Kattyar et al., 2022).

An optimal medication delivery system delivers a specified quantity of medicine to a target spot at the right pace and timing for the body's physiological demands. Thus, innovative drug delivery methods manage drug dose in a medically relevant range, convey drug content to a particular target region, and last longer (Singh et al., 2021). Pre-designed controlled drug release ensures effective drug content at the target location, avoiding hazardous side effects and boosting therapeutic advantages (Sivadasan et al., 2023).

For phytoconstituent bioavailability, new nano-carriers have been produced using various methods (Barani et al., 2021). Nanocarriers for phytoconstituents are usually vesicular drug delivery devices with active phytochemicals in spheres (Supraja and Mulangi, 2019). To transport drugs to target sites without metabolism or destruction, phytosomes, transferosomes, ethosomes, liposomes, colloidosomes, and others have been produced (Chivte et al., 2017).

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

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

Phytosome technology

Herbosomes, or phytosomes, are a new phyto-constituent that absorbs better topically, orally, and transdermally (Gaurav et al., 2021). In 1989, Italian nutraceutical and pharmaceutical business Indena created phytosome, a phospholipid complexation technique (Lu et al., 2019). "Phyto" means plant and "some" means cell-like (Kattyar et al., 2022). (Ghanbarzadeh

et al., 2016) 'Phyto' means bioactive fraction of phytosomal complex comes from plant and 'some' means complex structure is similar to cell. Hydrogen bonding links phytoconstituents to phospholipids, usually phosphatidylcholine (PC), in phytosomes (Gaurav et al., 2021). Standardized plant extract or hydrophilic phytoconstituents are integrated into phospholipid molecules to generate lipid-compatible vesicles in phytosomal complex (Singh et al., 2014).

Compared to herbal extracts and bioactive components, phytosomes are a unique formulation with several advantages. Bioactive chemical bioavailability, lipid solubility, and gastrointestinal solubility are improved using phytosome technology. Vasicine treats asthma and bronchitis and may dilate the bronchi. Vasicine bioavailability is limited due to low solubility and GIT absorption. Using phytosome technology boosted vasicine solubility and absorption, improving bioavailability (Kattyar et al., 2022). Benefits include increased cell membrane crossing, stability, prolonged administration, and protection from toxicity and chemical or physical degradation (Singh et al., 2014). Research shows phytosomes' better efficiency in dose reduction and pharmacological potential (Barani et al., 2021). Plantosomes improve transdermal medicine delivery and offer several cosmetic uses (Gaurav et al., 2021).

Hedyotis corymbosa, Nicotiana tabacum var. Virginia, Moringa oleifera, Punica granatum L., Geophila repens, Vaccinium macrocarpon, and Intsia In summary, phyto-phospholipid technology helps poorly absorbed phytochemicals and herbal extract (Anjana et al., 2017).

Structure of phytosomes

Phytosomes resemble cell membranes chemically (Ghanbarzadeh et al., 2016). Their production is caused by phospholipid polar heads and active phytoconstituents (Khan et al., 2013). These interactions between phytoconstituents and phospholipids generate phyto-phospholipid complexes with polar phospholipid heads but no two long fatty acid chains. Fatty acid chains move and encapsulate phytosome polar surfaces to create lipid-soluble surfaces (Ghanbarzadeh et al., 2016).

Phytosomes differ from liposomes

Diluted phytosomal complexes create cell-like agglomerates in water, resembling liposomes. Differentiating phytosomes from liposomes helps you realize their distinctiveness (Table 2). The bioactive substance in phytosomes is part of the membrane, whereas liposomes' active ingredient resides between membrane layers or in the water-soluble cavity. One phospholipid and one polyphenol molecule hydrogen-bonded together form a phytosomal unit. This links bioactive phytochemicals to the polar component of phospholipids, which are part of the cell membrane.

In the unit liposome, hundreds of phospholipids form a spherule with additional bioactive molecules that are segregated but not linked. Due to stable hydrogen bonding, phytosomes are more stable, absorbent, and bioavailable than liposomes. The best phytoactive compound-phospholipid molar ratios for phytosomes are 1:1 or 1:2. In liposomes, phospholipid molecules outnumber phytoactive compounds tenfold. Oral transport using liposomes is uncertain, although phytosomes improve it (Kidd, 2009; Ghanbarzadeh et al., 2016; Lu et al., 2019).

Table 2. Difference between phytosome and liposome

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

		bioactive compound
Stability	High	Lower than phytosome
Bioavailability	High	Lower than phytosome

Components of Phyto-phospholipid complex

Bioactive phytoconstituents

Researchers commonly classify plant extract bioactive chemicals by their greater in vitro biological activities than in vivo activities. Most bioactive chemicals are polyphenols (Lu et al., 2019). Herbal polyphenolic chemicals that are hydrophilic cannot pass cell membranes. Rutin and curcumin are lipid-soluble and cannot dissolve in aqueous gastro-intestinal fluid. Phytosomes promote membrane penetrability of water-soluble agents and polar phase solubility of lipid-soluble substances. Phytosomes also protect polyphenolic chemicals against hydrolysis, oxidation, and photolysis (Kidd, 2009).

Besides polyphenols, phospholipids may encapsulate several physiologically active plant extract components, including piperine, allicin, and evodiamine (Lu et al., 2019). Thus, phytosome technology works for all bioactive substances, not only polyphenols (Kidd, 2009).

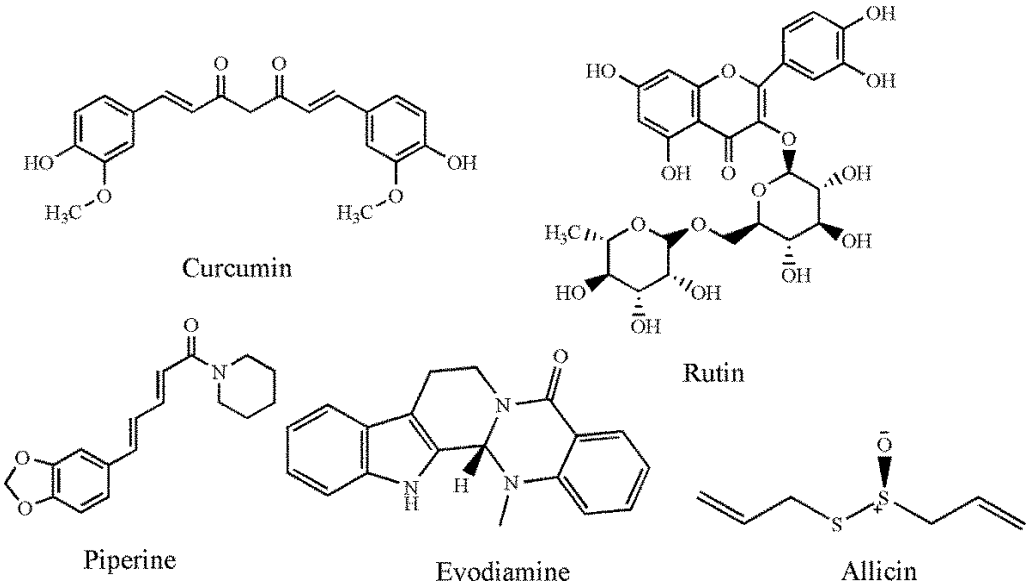

Figure 1. Structure of bioactive phytoconstituents

Phospholipids

Amphiphilic and biocompatible phospholipids are exceptional. Due to their unique properties, phospholipids are ideal pharmacological agents and have several drug delivery uses. The molecular structure of phospholipids is polar, phosphorus, and non-polar. Phospholipids have hydrophilic and hydrophobic acyl chains linked to alcohol. Phospholipids vary greatly according to polar head part, alcohols, and aliphatic chains. The backbone divides phospholipids into glycerophospholipids and sphingomyelins. Glycerophospholipids include PG, PI, PA, PS, PE, and PC. Main phospholipids used to make phytosomal complexes with two non-polar hydrocarbon chains and a polar part include PC, PS, and PE (Li et al., 2015).

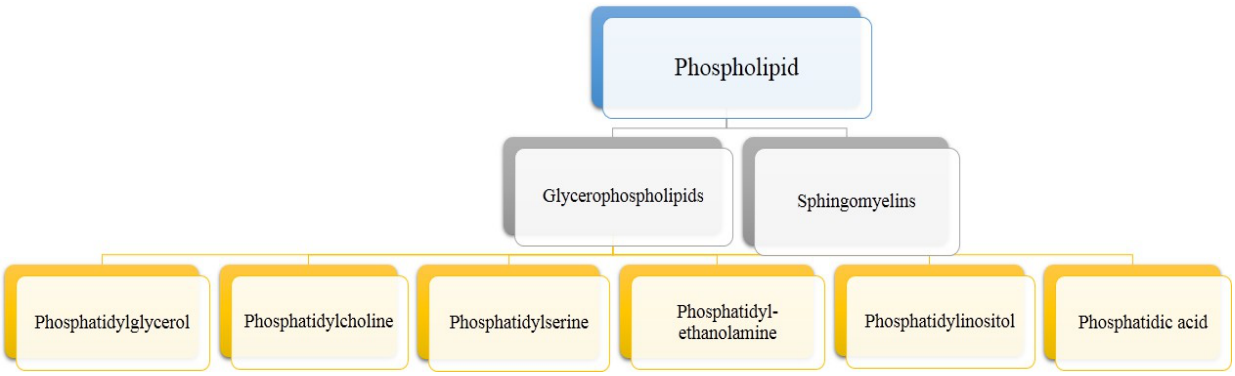

Figure 2. Classification of phospholipids (Li et al., 2015)

Phytosomes are predominantly made from phosphatidylcholine (Lu et al., 2019). Choline is hydrophilic and phosphatidyl is lipophilic in phosphatidylcholine (Agrawal et al., 2012). Its amphilic properties make it moderately soluble in aqueous and lipid solutions. It is biocompatible, low-toxicity, and essential to biological membranes. It protects the liver and treats fatty liver and hepatitis (Lu et al., 2019).

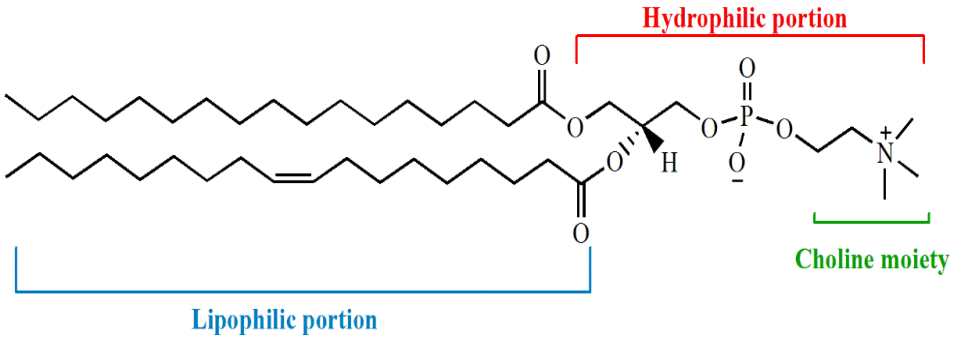

Figure 3. Structure of Phosphatidylcholine

Solvent system

Various solvents have been used to make phytosomes (Khan et al., 2013). To facilitate hydrogen bond formation, phytosomes are usually prepared in polar aprotic solvents (Telange et al., 2017; Vu et al., 2018). In aprotic solvents, hydrogen atoms cannot hydrogen bond with electronegative atoms. Traditional phytosome solvents include methylene chloride, aromatic hydrocarbons, cyclic ethers, and ethyl ethanoate (Khan et al., 2013). However, protic solvents like methanol and ethanol have supplanted them (Lu et al., 2019).

In protic solvents like ethanol and methanol, one hydrogen atom is directly bonded to an electronegative atom (Patel et al., 2009). Hydrogen bonds between active compounds and phospholipid molecules improve stability, entrapment efficiency, and cell membrane permeability, increasing bioavailability and efficacy (Permana et al., 2020). Hammam et al. (2017) found hydrogen bonding in methanol. Due to its high phytosome yield and minimal residues, ethanol is an efficient solvent (Patel et al., 2009). Many studies use ethanol to make Nicotiana tabacum var. Virginia leaf extract phytosomes (Chittasupho et al., 2023), naringenin-loaded dipalmitoylphosphatidylcholine phytosomes (Yu et al., 2020), and berberine-phospholipid complex-based phytosomes.

Despite most manufacturing methods using one solvent, mixed solvents have been documented. Studies have shown that phospholipid molecules and extract are dissolved in two solvents in mixed solvent systems. Mixed solvent systems include methanol and dichloromethane, diethyl ether and water, and ethanol and dichloromethane (Barani et al., 2021). Some pharmacological liposomal complexes operate in water or buffer because

phytosomal complexes have limited solvent interaction (Patel et al., 2009).

Recent research has employed supercritical fluid (SCF) to manipulate micronic and submicronic particle form, size, and other morphological properties. Supercritical anti-solvent technology uses a supercritical fluid, generally CO2, to reduce solute solubility in the solvent. It is promising for producing particles with regulated size distribution (Semalty, 2014). Supercritical anti-solvent precipitation formed puerarin-loaded phospholipid complexes (Li et al., 2008).

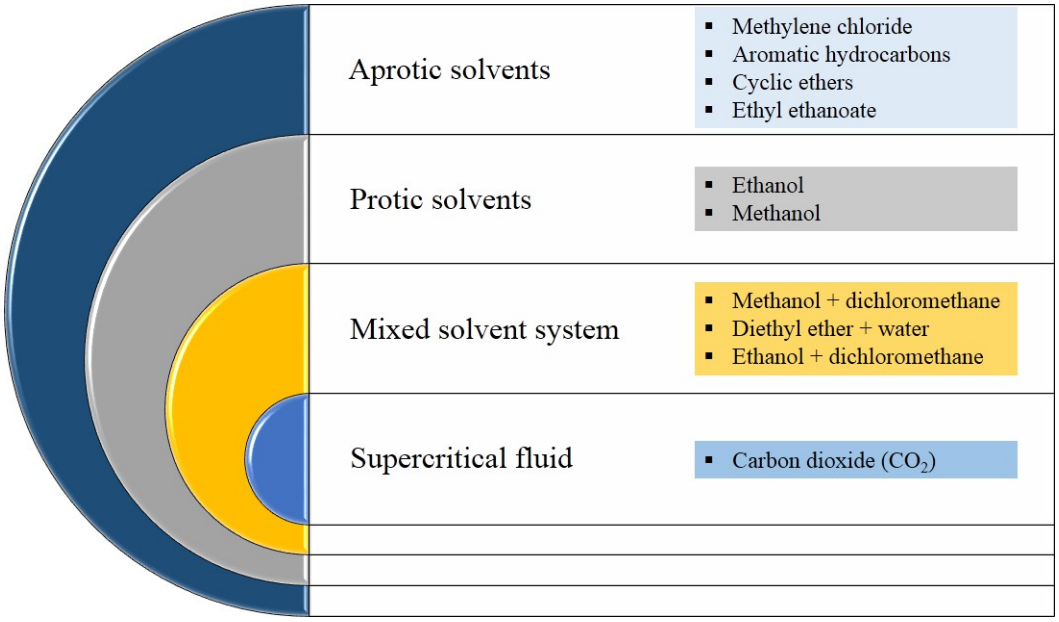

Figure 4. Solvent systems for phytosome formulation (Khan et al., 2013; Semalty, 2014; Lu et al., 2019; Barani et al., 2021)

Methods of formulation of phytosomes

Plant extract is converted into phospholipids, primarily phosphatidylcholine, to make phytosomes (Kattyar et al., 2022). Solvent evaporation, thin layer hydration, anti-solvent precipitation, co-solvent lyophilization, and salting-out are phytosome formulation methods (Anjana et al., 2017; Barani et al., 2021).

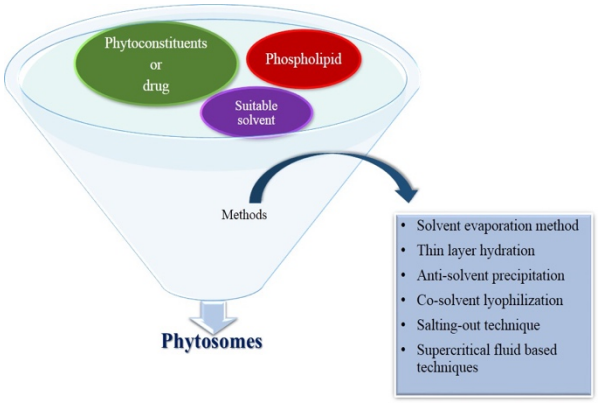

Figure 5. Fabrication of phytosomes (Anjana et al., 2017; Barani et al., 2021)

Solvent evaporation method

Solvent evaporation is a typical phytosome-making method. In a flask, active phytoconstituents and phosphatidylcholine in a defined stoichiometric ratio are heated at an optimal constant temperature for a particular period to dispersion in a suitable solvent. To make phytosomes, solvent is evaporated under vacuum (Lu et al., 2019). Solvent evaporation formed evodiamine-phospholipid complexes

(Liu, 2012). To create an efficient berberine delivery system, solvent evaporation and self-aggregation were used to make phytosomes (Yu et al., 2016). Solvent evaporation produced phytosomes-loaded methanolic leaf extract of Aegle marmelos (bael) (Dhase and Saboo, 2015).

Anti-solvent precipitation

In anti-solvent precipitation, phospholipid and medication are refluxed in a good solvent. After concentrating the mixture, additional solvent is added while stirring to precipitate. Filtered, collected precipitates are stored overnight in desiccators (Anjana et al., 2017). Antisolvent precipitation produced Allium cepa phospholipid complexes (Habbu et al., 2015), Scorpion venom-standardized quercetin-loaded phytosomal complexes (Alhakamy, 2022), and icariin phytosomes (Alhakamy, 2020).

Co-solvent lyophilization approach

Phospholipid and drug are refluxed independently in a solvent for co-solvent lyophilization of phytosomes. Both are gently combined until a clear solution forms. Further use of the homogenous mixture requires freeze-drying and storage in an airtight container (Anjana et al., 2017). Lyophilization produced kaempferol-loaded phytosomes (Telange et al., 2016).

Thin layer hydration method

Thin layer hydration mixes phytochemicals, phospholipid, and cholesterol in methanol and dichloromethane. A rotating evaporator evaporates the mixture to a dry thin sheet. To thoroughly remove organic solvents, nitrogen gas is usually passed over thin sheet. Next, vacuum drying totally evaporates organic solvents. The film is hydrated with distilled water (Anjana et al., 2017). Thin layer hydration was used to produce Vitis vinifera L. seed extract phytosomes (Surini et al., 2018).

Salting out method

Salting produced diosmin phytosomes. After salting out, diosmin and soy phosphatidylcholine phospholipid were combined in 35 ml of dehydrated ethanol, dimethyl sulfoxide, and chloroform in a 2:2:3 ratio. A magnetic stirrer was used overnight to stir the mixture, and 75 ml of n-hexane was added until precipitates formed (Freag et al., 2013). The salting out approach produced piperine phytosomes (Islam et al., 2022).

Supercritical fluid based techniques

Supercritical fluid is used for making 5–2000 nm particles. Gas anti-solvent technique, rapid expansion of supercritical solutions, supercritical anti-solvent method, compressed anti-solvent approach, and solution enhanced dispersion by supercritical fluids have been used to improve solubility of poorly soluble drug ingredients (Karataş and Turhan, 2015). Puerarin-loaded phospholipid complexes were prepared by supercritical anti-solvent precipitation, which was better than standard methods for drug-loaded phytosomes (Li et al., 2008).

Optimization

The Box–Behnken experimental design or another equivalent design optimizes phytosomes. An experimental strategy with three parameters was used to manufacture Icariin phytosomes. Molecular ratio of icariin to phospholipid, temperature, and refluxing duration were independent variables; vesicle size was the response. Design-Expert software generated 15 trials. Calculated precision ratio, adjusted, and anticipated coefficients of determination were utilized to choose a response model. We also found the best-fitting model equation. ANOVA was used to analyze observed responses and evaluate significance at $p < 0.05$. Three-dimensional and interaction plots were created to examine parameter interactions (Alhakamy et al., 2020).

Advantages of phytosome technology

- Phytosomes exhibits an excellent feature such as better absorption which leads to better bioavailability than simple plant extracts (Bhise et al., 2019). An improved absorption leads to a lower dosage of phytoconstituents required for a biological effect (Barani et al., 2021).
- Phytosomes are cell-like where all the important constituents of plant extract are prevented from the degradation by gut bacteria and digestive secretions (Nagar, 2019). Formation of phytosomal complexes

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

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

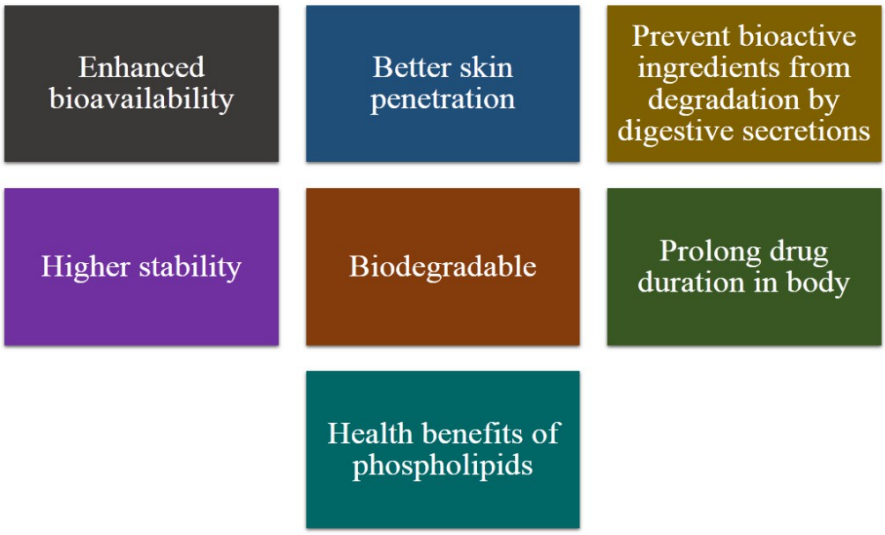

Figure 6. Advantages of phytosome technology

Marketed phytosomal products

Permana et al. (2020) found phytosomes to be effective nano-carrier drug delivery devices. Pharmaceutical companies have investigated phytosomes' biological activity, phytoconstituent bioavailability, and benefits (Barani et al., 2021). Table 2 lists commercialized phytosomes and their biological uses. However, many phytochemicals with the potential to treat life-threatening diseases have not been integrated into phytosomes (Gaurav et al., 2021). Milan-based Indena S.p.A. owns Phytosome® and all other trademarks (Karimi et al., 2015).

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

Sr. #	Trade name	Phytoconstituent complexed with phospholipid	Plant source	
1.	Greenselect® phytosomes	Epigallocatechin 3-O-gallate	Green tea	An anticancer and antioxidant agent
2.	Leucoselect® phytosomes	Procyanidolic oligomers	Grape seeds	Anti-oxidant and anticancer
3.	OleaselectTM phytosome	Polyphenolic compounds from essential oil of olives	Olea europaea L.	Prevent toxic oxidative reaction of low density lipoprotein cholesterol
4.	CasperomeTM	gum resin	Banksia serrata	Improve tissue distribution of boswellic acids
5.	Hawthorn phytosomeTM	Flavonoids	Crataegus species	Antihypertensive and cardiotonic
6.	Curcumin (Merinoselect) phytosomes	Polyphenol	Curcuma longa	Anticancer and improve bioavailability of curcuminoids
7.	Sericoside phytosome	Sericoside	Terminalia Sericea	Anti-wrinkles and soothing effects
8.	Ginkgoselect®	24 % flavono-glycosides	Ginkgo biloba	Provide protection to vascular lining and brain.
9.	Mirtoselect® phytosome	Anthocyanosides	Bilberry	Decrease abnormal permeability of blood vessel and improve capillary tone. These have high potential in managing venous insufficiency and retinal blood vessel issues.
10.	Sabalselect® (Palmetto) phytosome	Saw palmetto berries extract	Serenoa repens	Helpful for prostate normal functioning
11.	PolinaceaTM phytosome	Echinacosides	Echinacea angustifolia	It improves function of immune system in response to some toxic condition
12.	LymphaselectTM phytosome	Melilotus officinalis standardized extract	Melilotus officinalis	It is suggested for venous diseases
13.	Panax ginseng phytosome	Ginsenosides	Panax ginseng roots	Utilized as a food product
14.	Zanthalene phytosome	Zanthalene	Zanthoxylum bungeanum	Anti-itching, anti-irritant, and soothing effects

Recent advanced research in phyto - phospholipids complexation

Pharmaceutical companies and academics studied phytosome compositions' originality, biological activity, and polar phytochemical

bioavailability. The evidence supporting these formulations encourages researchers to continue their work. Clinical studies showing that standardized products are more effective than unformulated extracts or phytochemicals will help promote these technologies (Barani et al., 2021). Due to their biological benefits, silymarin, grape seed extract, quercetin, curcumin, ginkgo biloba extract, and others are gaining attention. The success of this method and the huge demand for herbal medications for illness treatment have led to additional study. Since phytosome technology was developed, several phytosomal compositions using medicinal plants and phytochemicals have been documented. Table 3 lists recent phytosomal formulations and their literature.

Table 4. Literature view of previous reported phytosomal formulations

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

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

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

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

Conclusion

The new phytosome approach is used to make plant-based medicines using phytochemicals of plant extract surrounded by phospholipid. Most bioactive components of herbal medicine are water-soluble, such flavonoids. Due to its lipid-soluble outer layer, phytosomes absorb more than typical herbal extracts, improving bioavailability. Additionally, the phospholipids used have medicinal advantages. Simple, non-conventional, repeatable phytosome formulation techniques exist. Many patents and marketable formulations of phytosomes have been authorized for unique procedures and uses. Many phytochemicals have been encapsulated as phytosomes, and more may benefit from similar formulations. Future study may show synergistic advantages when phytosomes are coupled with additional phytochemicals or drugs in nano-vesicles. Future research may benefit from phytosomes encapsulated with additional phytoconstituents or a medication and phytochemical in a nano-vesicle.

Future Outlook

Phytosome nanotechnology might revolutionize topical bioactive phytochemical delivery. Phytosomes, lipid-based nanocarriers, improve the pharmacokinetic and pharmacodynamic characteristics of polyphenolic compounds from plants, making this nanotechnology intriguing for innovative topical formulations. This nano-sized delivery technology may boost phytochemical bioavailability by penetrating biological barriers due to its unique physiochemical features (Alharbi et al., 2021). Originally used in cosmetics, phytosomes are now utilized to treat cancer, tumors, inflammation, heart disease, and liver diseases. With this new formulation technique, Phytosomes has reemphasized herbals' role in current medication targeting. Because they bind particular ligands and antigens to cellular sites, phyto-phospholipid complexes may be used for active and passive targeting. Thus, phyto-phospholipid complexes may cure osteoarthritis, cancer, and rheumatism. Advanced methods include supercritical fluid systems and pressure, temperature, and other conditions might restrict product dimensions. Products will target tumors and inflammation more effectively due to their greater penetration,

retention, and size. Using statistical tools like Box–Behnken design, factorial design, and others, variables like phytoactive or drug with phospholipid molar ratios, temperature, and others can be optimized to achieve the best drug release profile and entrapment efficiency (Khan et al., 2013).

Phospholipids have far higher bioavailability than chemically equivalent non-complexed forms. Pharmaceutical applications for the phyto-phospholipid complex are potential with physician and researcher support (Lu et al., 2019). This might open the door to using this method for additional medical objectives. Encapsulating phytochemicals like curcumin with effective medication delivery methods may provide eco-friendly and safe therapies for common human illnesses. Research is needed on the ingestion of entire curcumin nano-phytosomes for targeted organ delivery, including cancer (Ipar et al., 2019).

Several nano-technology-based cancer medication delivery systems have FDA clearance. Lipid-based nano-vesicles, a novel nanocarrier with a lengthy research history, have several advantages over conventional drug carriers in bioavailability, biocompatibility, cost, biodegradability, and raw material accessibility. By adding natural and synthetic anti-cancer drugs to nano-phytosomes, cancer treatment delivery systems will improve. Hydrophilic phytochemicals used in cancer therapy might change phytosome technology in nutraceuticals (Babazadeh et al., 2018).

Phytosome technology has several advantages over other dosage forms. Several pharmaceutical phytosomes are patented. This study shows that Phytosomes® have opened up new possibilities for pharmacological research and development (Agarwal et al., 2012). For formulation technology and hydrophilic plant compound applications, phytosome technology offers significant promise.

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