Review Article

Recent Trends and Future Prospects of Phytosomes: A Concise Review

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Sakure *et al.*: Advances in Phytosome Technology: Enhanced Bioavailability and Therapeutic Potential

Phytosome is a phospholipid based well-turned, self-assembled vesicular drug delivery system. It is an advanced form of herbal preparation that includes bioactive phytoconstituents of herbal extract surrounded and tied by a lipid. The phospholipid's molecular structure is composed of a head that is water-soluble and two tails that are fat-soluble. As a result of their dual solubility, the phospholipids function as an efficient emulsifier and act as a key component of our cell's membranes. Phytosomes are created with standardized plant extracts or phytoconstituents, such as flavonoids, terpenoids, tannins and xanthones, complexed with phospholipids like phosphatidylcholine. It exhibits significantly improved absorption profiles after oral administration due to enhanced lipid solubility that allows them to cross biological membranes, increasing their bioavailability. This article briefs about an updated overview of therapeutic potentials, patented technologies and recent formulations of phytosome drug delivery systems. The current review also highlights commercial availability, recent advanced research, and landmarks in the development of phytosomes and phytosome technology.

Key words: Phytosomes, phospholipid, herbal extract, bioavailability, phytopharmaceuticals

Medicinal plants and the therapeutic ingredients they contain have been used for many years to cure a variety of ailments[1-5]. The rising usage of herbal medications is mostly due to the fact that all human illnesses cannot be effectively treated by modern medicine, synthetic drug assurance and safety are receiving more interest and attention and many natural items are proven to outperform synthetic medications without side effects[6]. Due to their poor oral bioavailability, the clinical use of many active plant chemicals is debatable[7,8]. "Phyto" denotes a plant and "some" describes something that resembles a cell. Herbosomes, also known as phytosomes are vesicular drug delivery systems that improve the bioavailability of low-soluble medicines[9,10]. Phosphatidylcholine (or any other hydrophilic polar head group) and plant extracts react in an aprotic solvent to form phytosomes[11-13]. Numerous plant extracts have been the subject of chemical and pharmacological studies over the years to determine their chemical constituents and confirm traditional medicine's uses. Various bioactive elements of many plants are polar or water-soluble substances. But water-soluble plant substances (like flavonoids, tannins and terpenoids) are poorly absorbed either due to their large molecule size, which prevents passive diffusion or due to their poor lipid solubility, which severely limits their ability to cross lipid-rich biological membranes and results in poor bioavailability. When extracts are consumed orally, some of their contents could be degraded in the gastric environment. The compositions, biological functions and health-wellness properties of plant extracts and their derivatives have been well-established by phytochemical and phyto-pharmacological studies throughout the past century[8,14,15].

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The major components of the herbal extract are secure from being destroyed by digestive secretions and gut bacteria by creating a tiny cell in phytosomes formulations. Pharmacokinetic and pharmacological parameters of herbal extracts have been improved with phytosomes. Phytosomes have a greater ability to cross lipid-rich bio membranes and eventually reach the blood, making them more accessible than herbal extract[16].

Complex chemicals known as phospholipids are responsible for the building of cell membranes. Phospholipids are lipid molecules in which the glycerol is linked to two fatty acids, leaving the phosphate group to occupy the remaining space.

The most often used phospholipid is phosphatidylcholine, which is obtained from soybean (glycine max). By reacting 1-2 mol of phospholipids such as phosphatidylcholine, phosphatidylethanolamine or phosphatidyl-serine with 1 mol of a bioactive component (flavonoids or terpenoids) in an aprotic solvent, phytosomes are produced (dioxane, acetone, methylene chloride, ethyl acetate). It is common practice to create herbal extracts with flavonoid and terpenoid components because they are prepared to directly bind with the phosphatidylcholine moiety[15,17-19]. Phytosomes with phospholipids surrounding and securing hydrophilic bioactive phytoconstituents of herbs (phosphatidylcholine). It is made up of lipid bilayers (fig. 1).

CHARACTERISTICS OF PHYTOSOMES

Physicochemical characteristics:

A phytophospholipid complex is made up of a natural substance and organic phospholipids, such as soy phospholipids. By reacting stoichiometric concentrations of phospholipids and the substrate in the right solvent, one can create this complex. Based on spectroscopic data, it has been demonstrated that the primary interaction between phospholipids and the substrate is caused by the formation of hydrogen bonds between the polar head of phospholipids (i.e., the phosphate and ammonium groups) and the polar functionalities of the substrate[20-24].

Biological characteristics:

Phytosome, when taken orally, improves the active absorption of active substances as well as their systemic bioavailability[25]. These herbal products are more advanced than traditional herbal extracts and are more effective. Phytosome's pharmacokinetics are superior to those of straightforward herbal medicines[26].

ADVANTAGES AND DISADVANTAGES OF PHYTOSOMES

Advantages of phytosome over conventional dosage form:

Improved absorption: Plant extracts or bioactive components have dramatically increased bioavailability because of their complexation with phospholipids and better intestinal absorption (fig. 2)[24,27].

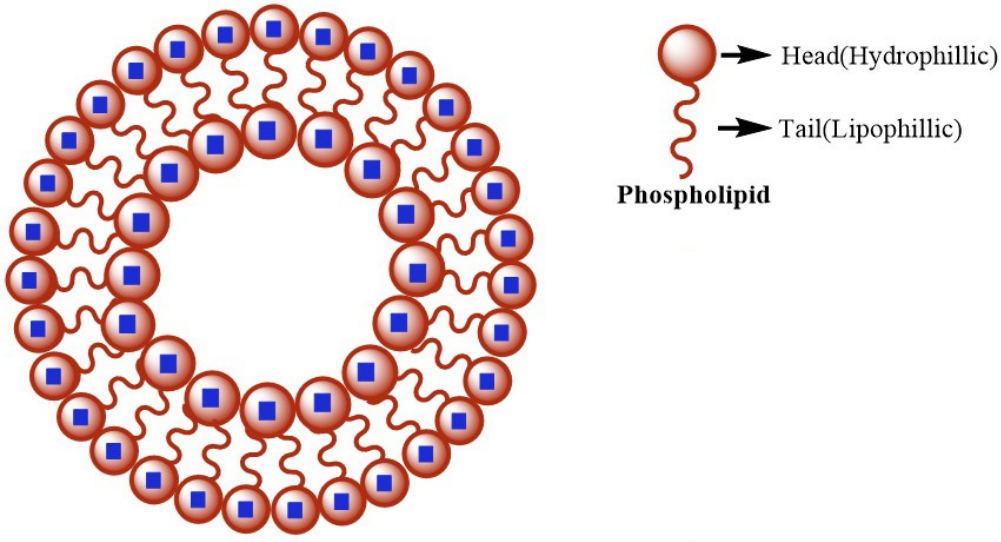

Fig. 1: Structure of phytosome[15,20,21]
Note: (◆) Drug and (🔴) complex

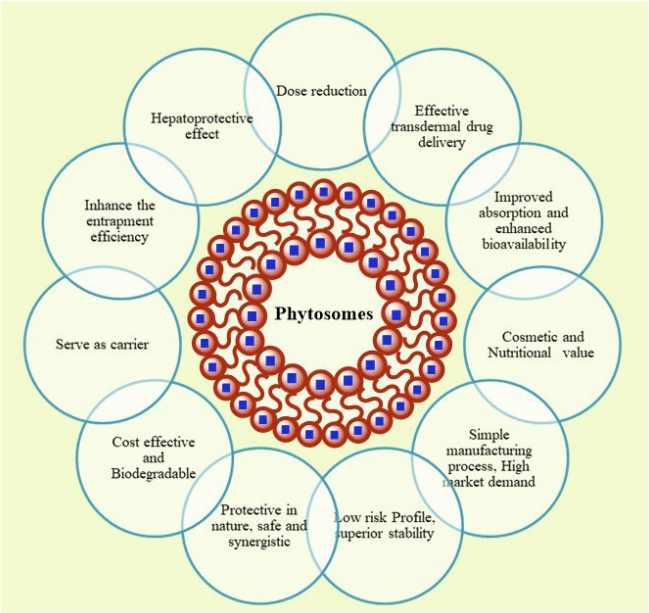

Fig. 2: Benefits of phytosomes over conventional dosage forms[15]

Cosmetic use: The components of phytosomes are all permitted for use as pharmaceutical and cosmetic aids and the formulation of phytosomes is safe[28,29]. They can also be utilized to improve the drug's penetration into the skin for transdermal and dermal delivery[30]. They have better skin penetration and a high lipid profile, making them suitable for widespread application in cosmetics. Functional cosmetics based on phytosomal compositions are possible[28].

Protective in nature: Because phytosomes can easily make liver-protecting flavonoids accessible, they have been employed to administer them. Additionally, because phosphatidylcholine is also hepatoprotective, it works in concert with other substances to protect the liver[22].

Cost-effective: When it is utilized to protect the skin against external or internal risks of every day and stressful environmental situation, this method offers cost-effective phytoconstituent delivery and synergistic advantages[28].

As a carrier: Phytosome technology involves phosphatidylcholine, a crucial component of the cell membrane that serves as a transit and nurtures the skin[22].

Improve the entrapment efficacy: Drug entrapment is not a concern at the time of preparation of the phytosome. Additionally, the entrapment efficiency is great and more over-predetermined as the drug itself produces vesicles after conjugating with lipids[22].

Improves stability: Because of the chemical linkages which have been created between the phosphatidylcholine molecules and the phytoconstituents, they have a superior stability profile. The phytosomal method can be readily commercialized because it is passive and non-invasive[22].

Dose reduction: The primary constituent's enhanced absorption results in a lower dose requirement. To obtain apt effects, they can also be administered in lesser doses.

Low-risk profile: Scientific literature is well-researched on the toxicity profiles of the phytosomal components, therefore there is no risk associated with this method for large-scale medication development.

Other advantages:

In addition to having a higher drug complexation rate, phyto-phospholipid complexes are also easier to prepare[31,32]. Additionally, phyto-phospholipid complexes have greater stability due to the phosphatidylcholine molecule's capacity to chemically interact with plant extracts. Phyto-phospholipid complexes increase liver targeting by making bile more soluble in its active components[1,33]. Naringenin has a short half-life and due to quick elimination from the body it needs to be administered frequently. To increase the duration of naringenin in the bloodstream, phospholipid complexes of it were created[34].

As per other different research, the phospholipid significantly increased the plasma concentration of andrographolide, as well as that effect lasted for a longer time. Additionally, andrographolide-phospholipid complexes have 3.34 times longer half-life than pure andrographolide[35].

Disadvantage of phytosomes:

Rapid elimination of phytoconstituents of phytosome may diminish the target drug concentration and indicate the unstable nature of these phytosomes, which is a major drawback[17,36,37].

Influencing factors for phytosome preparation:

Phytosome preparation involves the development of a delivery system that enhances the bioavailability and efficacy of phytochemicals, particularly plant extracts. Several factors influencing the preparation of phytosomes were mentioned below[38,39].

Properties of phytochemical: The physicochemical properties of the phytochemicals, such as solubility, lipophilicity and molecular weight play a crucial role in phytosome preparation. These properties determine the compatibility of the phytochemicals with the phospholipids used to form phytosomes[40].

Selection of phospholipid: Phytosomes are typically formed by complexing phytochemicals with phospholipids. The choice of phospholipid is crucial as it affects the stability, solubility and compatibility of the resulting phytosomes. Different phospholipids, such as phosphatidylcholine, phosphatidylserine and phosphatidylethanolamine can be used based on the specific requirements of the phytochemical[13].

Complexation techniques: Various methods can be employed to achieve the complexation of phytochemicals with phospholipids including solvent evaporation, solvent injection, thin-film hydration and supercritical fluid technology. Each technique has its advantages and limitations and may be chosen based on the specific characteristics of the phytochemical and desired phytosome properties.

Solvent selection: Solvents are used to dissolve both the phytochemicals and phospholipids before the complexation process. The choice of solvent depends on the solubility of the phytochemical and the phospholipid. Common solvents include ethanol, chloroform, methanol and their combinations[41].

Ratio of drug-to-phospholipid: The ratio of phytochemicals to phospholipids is an important factor that influences the formation of phytosomes. The appropriate drug-to-phospholipid ratio ensures efficient complexation and stability of the phytosome[42].

Process parameters: Parameters such as temperature, pH and stirring speed during the preparation process can significantly affect the characteristics of the phytosomes. Optimizing these process parameters is essential to achieve desired phytosome properties, such as particle size, zeta potential and drug-loading efficiency[43].

Stabilizers and excipients: Additional excipients and stabilizers such as surfactants, antioxidants, and cryoprotectants may be incorporated into the phytosome formulation to enhance stability, prevent aggregation and improve shelf life[44].

Method of preparation of phytosomes:

When polyphenolic phytoconstituent is complexed with a phospholipid it creates phytosome®. The observed mass ratios range from 1:1.5-1:4, depending on the product[45]. Depending on the protocol used, alternative phytosome®[46-58] preparation techniques and the resultant complex may be used. As a result, three distinct complexes of silybin-phospholipid have been revealed and the phospholipid complex of curcumin formed in an aprotic solvent shows notable differences from the one prepared in protic solvent[47,59,60]. Two of them-Silipide (IdB 1016)[55], pharmaceutical grade phytosome® that undergone detailed characterization[61] and siliphos® were made in aprotic solvents, whereas a third silybin-phospholipid complex was made in protic solvents[57]. As it is seen for *Ginkgo biloba* extracts, where the regular phosphatidyl-choline complex is going by the name Ginkgoselect Phytosome® and the Phytosome® extract using phosphatidylserine, this complex is known as Virtiva®. Different phospholipids provide distinct complexes (fig. 3).

Characterization and evaluation of phytosomes:

Solubility and partition coefficient are crucial parameters for characterizing active components, active constituent phyto-phospholipid complexes and physical mixes, it is important to determine solubility in water or organic solvents and the n-octanol/water partition coefficient[1,62]. Phytosomes or herbosomes often display increased

lipophilicity and hydrophilicity compared to the active ingredients[63]. Rahila confirmed that compared to embelin and its corresponding physical mixes, embelin phytosomes had a higher solubility in n-octanol and water[64].

Drug content:

By accurately weighing 100 mg of phytophospholipid complex is loaded and dissolving it in 10 ml of solvent, the drug concentration of the phytosome loaded can be ascertained. After the proper dilution, a Ultraviolet (UV) spectrophotometer may be utilized to measure absorbance. The formula listed below is applied for the estimation of the percentage strength of the drug[38,65].

Drug content (%)=total amount of drug-amount of free drug/total amount of drug×100

Complexation and molecular interactions between phytoconstituents and phosphatidylcholine in solution have been studied by different spectroscopic techniques like Infrared (IR), Nuclear Magnetic Resonance (NMR), Differential Scanning Calorimeter (DSC) and thermal gravimetric analysis[25,66-68]. For visualization of structure and its molecular size and stability, various techniques like scanning electron microscopy, transition electron microscopy and zeta potential measurements are routinely used.

Difference between phytosomes and liposomes:

In a liposome, the key ingredient is liquidized in the media that fills the cavity or in the layers of the membrane, but a phytophospholipid complex or herbosome is a component of the membrane that is joined by chemical bonds to the polar head of the phospholipids[44,69]. Liposomes, which are currently typically employed for cosmetic purposes, contain several hundred phospholipid molecules for trapping. In the creation of phytosomes, 1-4 phospholipid molecules engage with the phytochemicals that are chemically linked with one another[70]. Due to this distinction, phytosomes are significantly more readily absorbed than liposomes, as shown in fig. 4. In cosmetic items, phytosomes are more advisable over simple vesicles[9,71]. In phytosomes, the molecules are bonded together having a chemical bond. While the liposomes are an assemblage of numerous phospholipid molecules that can surround other phytoactive compounds but do not explicitly connect to them and have no chemical linkage[72].

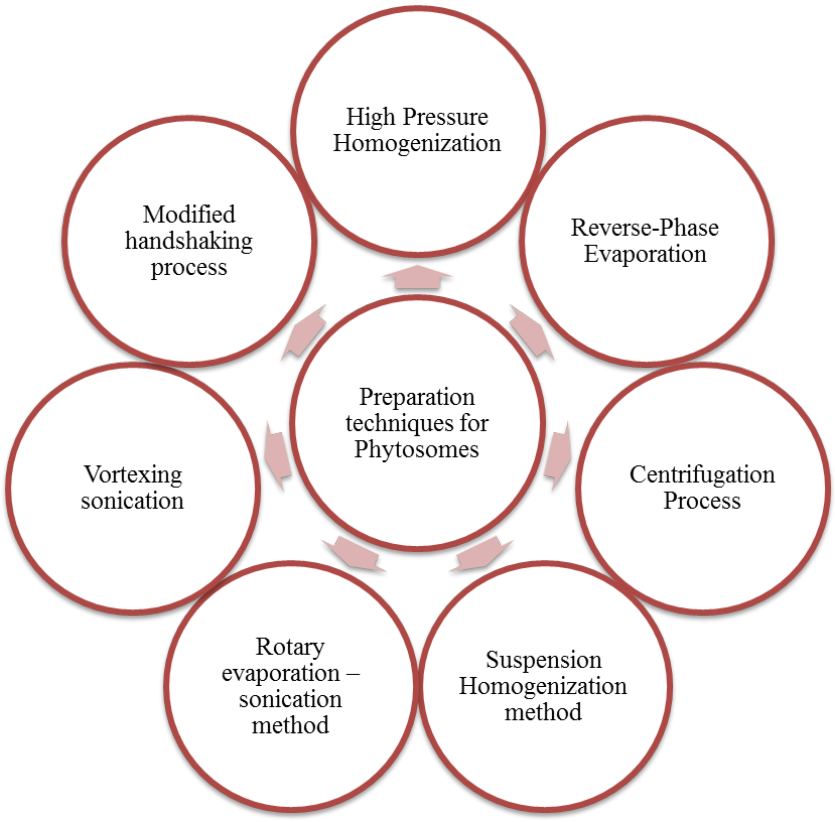

Fig. 3: Methods of preparation of phytosome

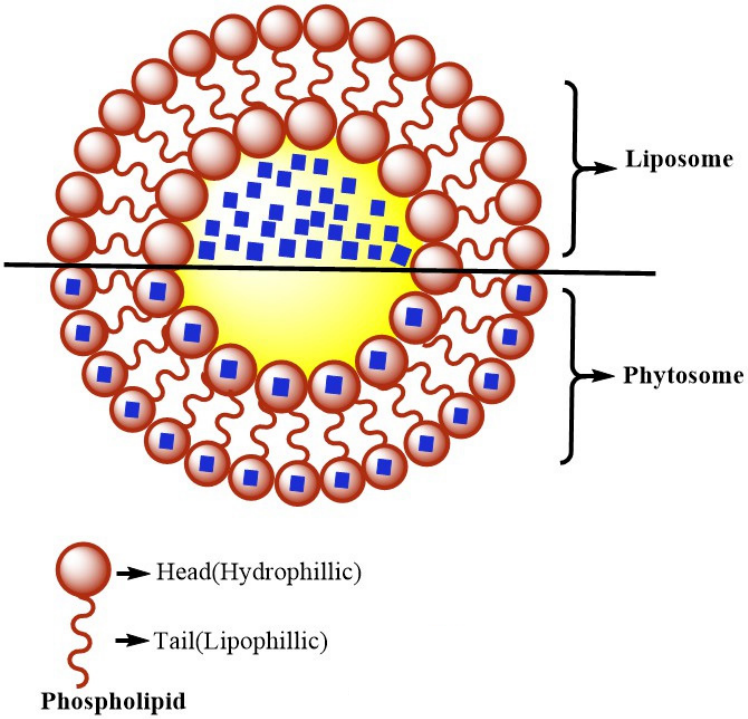

Fig. 4: Schematic representation between liposome (upper segment) and phytosome (lower segment)
Note: (◆) Water soluble free drug and (♀) phospholipid drug complex

Significance of phytosome in drug delivery application:

Phytosomes are complex compounds formed by binding a phyto-extract or its constituents to phospholipids, primarily phosphatidylcholine, on a molecular level. This unique structure significantly improves the absorption and bioavailability of the phytoconstituents, making phytosomes a promising tool in drug delivery applications. The significance of phytosomes in drug delivery applications can be understood in the following ways:

Enhanced solubility: Phytosomes also enhance the solubility of phytoconstituents. Many phytoconstituents are poorly soluble in water, which can limit their absorption in the gastrointestinal tract. Phytosomes can enhance the solubility of these compounds, thereby improving their absorption and efficacy. This is particularly beneficial for phytoconstituents with significant therapeutic potential but limited solubility[73].

Enhanced stability: Phytosomes also offer improved stability compared to conventional herbal extracts. The phospholipid shield in the phytosome structure protects the active ingredient from destruction by gastric juices and enzymes in the gut. This stability ensures that a larger proportion of the active ingredient reaches the systemic circulation, further enhancing the therapeutic effect of the phytoconstituents[74].

Improved bioavailability: The primary advantage of phytosomes is their ability to enhance the bioavailability of phytoconstituents. Many phytoconstituents, despite their therapeutic potential, have poor absorption and rapid metabolism that limit their bioavailability. Phytosomes improve the absorption of these compounds by facilitating their transport across the lipid-rich outer layer of the intestinal cells, thereby enhancing their bioavailability. This is a significant advantage as it allows for the full therapeutic potential of the phytoconstituents to be realized[75].

Targeted delivery of phytoactives: Another significant advantage of phytosomes is their potential for targeted drug delivery. Phytosomes can be designed to deliver drugs to specific parts of the body, improving the therapeutic effect and reducing side effects. This is particularly useful for drugs that are intended to act on specific organs or tissues. By delivering the drug directly to the site of action, phytosomes can maximize the therapeutic effect while minimizing potential side effects[76].

Phytosomes potential as an innovative drug delivery method:

Phytosomes are used to treat several illnesses, including cancer, heart disease and liver disease. Phytosomes have a broad area appertaining to additional applications, namely anti-inflammatory, lipolytic, vasokinetic as well as anti-edema agents. Additionally, it functions as an antioxidant, immunomodulator, nutraceutical, etc.[77-79].

Application of phytosomes in cancer:

Cancer continues to be a major global health concern, necessitating the development of innovative therapeutic approaches. The application of phytosomes, holds tremendous potential in the field of cancer treatment, offering improved efficacy and targeted delivery of bioactive compounds[76]. In this regard, silibinin, extracted from silymarin, has been reported to exhibit good anticancer activity[80]. However, low bioavailability and limited solubility have its therapeutic use. Comparatively, phytosome drug delivery systems enhanced the apoptotic actions of silibinin[81]. In breast cancer cells, the dissemination of silybin phytosomes was reported to be 4 times higher than the dispersion of silybin. In addition, cancer cells accumulated much more silybin phytosomes than typical healthy cells. According to previous research, phytosomes increase the bioavailability of phytochemicals, trigger apoptotic cell death and enhance the sustained delivery of phytoconstituents[82]. Mitomycin C-soybean (MMC) loaded phytosomes, another anticancer phytoactive, were shown to have improved stability and sustained release of MMC, resulting in a significant increase of cellular toxicity in murine hepatic carcinoma cells[83]. Phytosomes are ideal systems for enhancing the bioavailability of anticancer phytoconstituents. The poor bioavailability of *Terminalia arjuna* restricts its applicability as anticancer therapy. However, *Terminalia arjuna* extract-loaded phytosomes significantly induced significant cytotoxicity in breast cancer cells (MCF-7)[84]. Phytosomes are highly effective in the transport of both single phytoactives and combinations of phytochemicals, with enhanced permeability into cancerous cells. Phytosomes play a crucial role in enhancing cellular toxicity by altering the intracellular redox state and facilitating the passive targeting and reduced expression of many transcriptional regulators.

Curcumin, a known polyphenolic anticancer phytoconstituent found in *Curcuma longa*, has been successfully co-delivered with other therapeutic moieties. In a research, conjugates of curcumin with scorpion venom showed potent cytotoxic activity against PC3 carcinoma cells[85]. Decreased expression of Epithelial cadherin (E-cadherin or cadherin-1) signal transduction channels and reduced expression of Wnt pathways by curcumin-phytosomes co-delivered with 5-fluorouracil was shown to decrease colorectal cellular proliferation and metastasis[86]. Curcumin phytosome combined with gemcitabine led to a more than 61 % disease control rate and 27 % response rate in similar research. Studies comparing phytosomal therapy to other pancreatic cancer treatments revealed it to be both more secure and more effective[87].

Application of phytosomes in cardiovascular protection:

Cardiovascular diseases pose a significant burden on global healthcare systems, highlighting the need for novel therapeutic strategies. The application of phytosomes, an advanced drug delivery system, has emerged as a promising approach to the management of cardiovascular diseases. *Ginkgo biloba* phytosomes were tested for their cardioprotective effects in a rat model of Isoproterenol (ISO) induced cardiotoxicity. Histopathological analyses demonstrated that *Ginkgo biloba* phytosome significantly reduced ISO induced myocardial necrosis. Increases in endogenous antioxidants and a reduction in myocardial necrosis collectively demonstrated a cardioprotective effect[88]. The inflammatory effects of *Ginkgo biloba* phytosome and lipoic acid on Vein Endothelial Cells (VEC) obtained from patients at varying stages of cardiovascular disease were studied by Tisato *et al.*[87]. Cell adhesion molecules ICAM-1 and VCAM-1 decrease verified the anti-inflammatory effects of *Ginkgo biloba* derivatives and lipoic acid. *Ginkgo biloba* phytosome reduced both the baseline and TNF-α induced levels of motif C-X-C motif chemokine Ligand 10 (CXCL10) and Regulated upon Activation, Normal T cell Expressed and Secreted (RANTES)[89]. The therapeutic effectiveness of *Ginkgo biloba* phytosome, for the treatment of Raynaud's Phenomenon (RP), was studied by Muir *et al.*[88] and the group. *Ginkgo biloba* phytosome

was demonstrated to significantly reduce the frequency of RP episodes per week compared to placebo ($p<0.00001$)[90]. In terms of hemorheology, no major differences could be found between the two groups.

Application of phytosomes in the nervous system disorders:

Nervous system disorders encompass a wide range of conditions that significantly impact the quality of life. In recent years, the application of phytosomes, a cutting-edge drug delivery system, has gained attention as a potential therapeutic avenue for the treatment of various nervous system disorders, offering improved bioavailability and targeted delivery of neuroactive phytoconstituents. Several studies have reported the bioavailability of phytosomes in animal models, with a particular focus on the tissue distribution of the active components, in comparison to similar unformulated products. Scientists investigated the possibility that antidepressant-like activity could be improved by increasing the permeability of a phytoconstituent through phytosomes. In this regard, phytosome enriched with a water extract of *Annona muricata* exhibited enhanced permeability across the blood-brain barrier by inhibiting monoamine oxidase B[91]. Curcumin loaded phytosomes have also presented enhanced therapeutic activity against nervous system disorders. Curcumin-phytosome has been reported to decrease glial activation *in vivo* models of chronic glial activation (GFAPIL6 mice)[92]. The greater dose of *Centella asiatica* phytosome, delivered to adult male rats counteracted cognitive impairment and promoted Brain-Derived Neurotrophic Factor (BDNF) elevation in the prefrontal cortex. When the preference index was raised, BDNF expression was also raised in the Norwegian Tenecteplase Stroke Trial (NOR-TEST). Furthermore, no treatment-related adverse events were reported[93]. Similar findings were reported by Sbrini *et al.*[92], who found that a preparation including extracts of *Centella asiatica* and *Curcuma longa*, when given chronically to rats, influenced local protein synthesis *via* the modification of the BDNF-mTOR-S6 pathway.

Application of phytosomes in respiratory diseases:

Phytosomes have gained significant position in the treatment of respiratory disease. With this in mind, a gingerol phytosome conjugating with chitosan has been tested by Singh *et al*.[93], for the treatment of respiratory infection both *in vitro* and *in vivo* settings. The phytosome complex enhanced gingerol oral absorption *in vivo* and had a significant sustained-release profile. When tested on Gram-positive and Gram-negative bacteria causing respiratory infections, the pharmacodynamic parameters showed long-lasting antibacterial and considerable anti-inflammatory activity[94,95]. Yu *et al*.[94] developed a novel phytosome to improve the pulmonary bioavailability of naringenin. Using a dry powder inhalation method, the pharmacodynamics and related mechanisms underlying the phytosomes loaded with naringenin were studied in rats with acute lung damage. These phytosomes mitigated lung injury when inhaled directly by rats. The data showed that Natriuretic Peptide Downstream Pathway Inhibitors (NPDPIs) alleviated pulmonary edema by lowering fluid exudation and the production of cytokines such Cyclooxygenase-2 (COX-2) and Intercellular Adhesion Molecule-1 (ICAM-1). Loading of naringenin inside phytosomes, amplified their anti-oxidative stress effects on rats[96]. Clinical trial studies have also confirmed the applicability of phytosomes in respiratory diseases. In this context, the effect of quercetin phytosome was tested in small research on healthy people who experienced mild to moderate asthma attacks and rhinitis. Quercetin phytosome performed better than the placebo group in terms of preventing and relieving symptoms during the day and night, preserving higher peak expiratory flow and minimizing its variability while keeping a solid safety profile[97].

Application of phytosomes in wound healing:

Despite advances in tissue regeneration procedures, secondary infection, prolonged healing of wounds and immunocompromised conditions can create difficult scenarios. Phytosomes, lipid-based nanoparticles containing plant-derived compounds, offer a promising approach to wound healing. In this context, sinigrin-phytosomes was demonstrated to promote considerable wound healing in human keratinocytes (HaCaT). Compared to sinigrin alone, sinigrin-phytosomes healed the wound fully (100 %) at 42 h[98]. Pegylated phytosomes were tested for their wound healing abilities in periodontal ligament fibroblasts by Al-Samydai *et al*.[97]. Pegylated phytosomes containing 6-gingerol considerably

accelerated the healing process. When compared to 6-gingerol alone, phytosomes suppressed the expression of pro-inflammatory mediators in breast cancer cells. *Calendula officinalis* enhanced phytosomes were developed by Demir *et al*.[98] and their wound healing properties were evaluated. In normal human dermal fibroblasts, phytosomes increased wound closure by >50 % as compared to plain phytosomes and *Calendula officinalis*.

In another study, in the Wistar rat excision models, *Onosma echioides* phytosomes (gel) dramatically accelerated wound healing (>98 %) compared to the control and standard. The amount of collagen was also dramatically increased by phytosomes compared to the control group. Increases in hydroxyproline levels are indicative of successful collagen synthesis[99-101]. It is evident that phytosomes improve the wound healing properties (*in vivo* and *in vitro*) of phytochemicals, both in excision and incision wound models. Tremendous research work is going on the phytopharmaceuticals, especially on the development of phytosomes from plant extract and its constituents due to their improved bioavailability[98]. Susilawati *et al*.[100] tabulated some of the recent research on phytosomes in drug delivery (Table 1)[100-118].

Patented phytosome-related technologies:

Numerous academic and industrial scientists have created phytosome compositions and discovered novel techniques. Table 2, lists several patents linked to novel technologies and phytosomes[12,47,51,54,119-128].

TABLE 1: RECENT FORMULATION OF A PHYTOSOME DRUG DELIVERY SYSTEM

Carrier	Pharmaceutically active ingredients	Phytosome preparation method	The goal of the study	Reference
Phosphatidylcholine	The root extract of *Clerodendron*	Thin film hydration method	Anticancer	[103]
Hydrogenated phosphatidylcholine phospholipon 90H	Extract of *Terminalia*	Solvent evaporation and precipitation method	Antihyperlipidemic	[104]
L-α-phosphatidylcholine and cholesterol	*Trigonella foenum-graecum*	Thin film hydration	Rheumatoid arthritis	[105]
Lecithin soya 30 % and cholesterol	*Tecomella undulata*	Solvent evaporation	Antitumor activity and several diseased conditions linked to the liver, spleen and abdomen	[68]
Phospholipid complex	Gallic Acid (GA, 3,4,5-trihydroxy benzoic acid)	-	Hepatoprotective agent	[105]
Phospholipid complex	*Boswellia*	-	Complementary intervention in asthmatic patients	[106]
Dipalmitoylphosphatidylcholine (DPPC), Cholesterol (CHOL) and Polyethylene Glycol 2000-Distearoylphosphatidylethanolamine (PEG2000-DSPE),methoxy-PEG2000-DSPE (mPEG2000-DSPE)	Silinin and glycyrrhizic acid	Thin film hydration	Anti-tumor agent	[107]
Phospholipid complex	Green select	-	Borderline metabolic syndrome	[66]
Soy Phosphatidylcholine (SPC)	Silymarin	Solvent evaporation	Hepatoprotective agent	[108]
Phosphatidylcholine	*Citrullus colocynthis* L, *Momordica baisamina* and *Momordica dioica*	Solvent evaporation	Antidiabetic agent	[42]

Phosphatidylcholine hydrogenated	Sinigrin	Solvent evaporation, thin film hydration	Wound healing agent	[109]
Phosphatidylcholine	Mitomycin C-soyabean	Solvent evaporation	Antiproliferative and anticancer agent	[83]
Phosphatidylcholine-folate	Mitomycin C-soyabean	Solvent evaporation	Folate-targeted drug delivery	[110]
Soybean phospholipids	Silybin	High-pressure homogenization	Hepatoprotective agent	[111]
Phospholipon	Apigenin	Solvent evaporation	Antioxidant	[112]
L-a-phosphatidylcholine hydrogenated (soyabean)	Sinigrin	Thin film hydration	Wound healing agent	[113]
Phosphatidylcholine	*Trichosanthes cucumerina* Linn. and *Abrus precatorius*	Solvent evaporation	Hair growth promoting agent	[114]
Lecithin delivery form	Boswellic acid	-	Anti-inflammatory	[115]
Phospholipid complex	Green select	-	maintenance of weight	[116]
Phosphatidylcholine	Soybean (Glycine max L. merrill)	Solvent evaporation, cosolvency and salting out	Combat or control obesity	[117]
Phospholipid-hyaluronic acid	L-carnosine	Solvent evaporation	Ocular delivery	[118]

TABLE 2: PATENTS RELATING TO PHYTOSOMES ON THE DEVELOPED TECHNOLOGIES

Patent no. (year of grant)	Title of the patent	Novelty/innovation	Reference
WO2009/101551 (2009)	Curcumin phospholipid complexes have improved bioavailability	Curcumin phospholipid complexes deliver a larger level of parent agent to the system than curcumin that has not been complexed	[47]
EP I844785 (2007)	Phospholipid complexes of olive fruits or leaf extract have improved bioavailability	Using phospholipid complexes, the bioavailability of olive fruit/leaf extracts is increased	[47]
EP I8I3280 (2007)	Compositions comprising *Ginkgo biloba* derivatives for the treatment of asthmatic and allergic conditions	Compositions of the *Ginkgo biloba* fraction obtained for the treatment of allergies and asthma	[119]
US/2007/00I5698 (2007)	Treatment of skin and wound repair, with thymosin β-4	The preparation created with thymosin 4 for wound healing	[120]
US769I422 (2007)	Oral compositions for the treatment of cellulite	Oral and cosmetic pharmaceutical Formulation incorporating *Centella asiatica* triterpenes, extracts of *vinifera*, and *Ginkgo biloba* flavonoids in the free or complexed form with phospholipids	[121]
EP I690862 (2006)	Fatty acid monoesters of sorbityl furfural and compositions for cosmetic and dermatological use	For particular antihydroxyl radical activity, the selected fatty acid monoesters of sorbityl furfural serve as lipophilic agents	[122]
EP I640041 (2006)	Cosmetic and dermatological composition for the treatment of aging or photo-damaged skin	The topical cosmetic or dermatological preparation for treating wrinkles that contain at least one constituent that promotes the synthesis of collagen	[123]

WO/2004/04554I (2005)	Soluble isoflavone composition	The solubility, textural properties, flavor, and color of the formulation were improved by isoflavone compounds	[124]
EP I2I4084 (2004)	An antioxidant preparation based on plant extracts for the treatment of circulation and adiposity problems	For the treatment of varicose veins, phlebitis, hemorrhoids, arteriosclerosis, and high blood pressure, a formulation of plant extracts with antioxidant activity was produced	[125]
US6297218 (2001)	Phospholipid complexes prepared from extracts of *Vitis vinifera* as an anti-atherosclerotic agent	Phospholipid complexes made from *Vitis vinifera* extract are used to cure and prevent atherosclerosis	[126]
EP 044I279 (1991)	Bilobalide phospholipid complexes, their applications, and formulations containing them	Complexes of synthetic or natural phospholipids and this bilobalide and use them to treat inflammation and neuritic processes. Complex demonstrated higher bioavailability than free bilobalide	[127]
EP 0464297 (1990)	Complexes of neolignane derivatives with phospholipids, the use thereof and pharmaceutical and cosmetic formulation containing them	Complexes of lipophilic extracts from the *Krameria* or *Eupomatia* plant genus and some neolignanes isolated from those extracts demonstrated antibacterial, antimycotic, and antiradical activities. It might be an effective preservative in cosmetic preparations	[128]
EP 0283713 (1988)	Complexes of saponins with phospholipids and pharmaceutical and cosmetic compositions containing them	Saponins' improved bioavailability makes them appropriate for use in cosmetic, medicinal, and dermatological applications when combined with natural phospholipids	[51]
EP 0209038 (1988)	Complexes of flavonolignans with phospholipids, preparation thereof, and associated pharmaceutical compositions	Creates lipophilic complexes of silidianin, silybin, and silicrist. The complex has strong gastrointestinal absorption followed by increased plasma levels. Complex useful for treating both acute and chronic liver disorders	[54]
EP 0275005 (1983)	Complex compounds of bio-flavonoids with phospholipids, their preparation and use, and pharmaceutical and cosmetic compositions containing them	As compared to free flavonoids, complex compounds of flavonoids with phospholipids have higher lipophilia, enhanced bioavailability, and medicinal effects	[12]

Commercial products of phytosomes and commercialization challenges:

Phytosomes are regarded as effective mechanisms for delivering nanocarriers[129]. But from product creation to successful commercialization, there is a long way to go. Despite all the benefits, only some of the phytosomal formulations have been released to the market[130]. A major obstacle to the commercialization of phytosomes is proving their safety after creating an efficient formulation. Because phytosome's structures are physiologically inert, it is appropriate to introduce them into the human body with no worrying about their safety or immunological effects[131]. Prior to their sale, it is important to establish certain parameters for their nano size, including bioaccumulation, biocompatibility, metabolism and excretion[132]. The potential of phytophospholipid complex to bind to biological membranes and passively target healthy cells should be taken into account as another aspect. It has been also observed that phospholipids (lecithin) had been shown to promote proliferation in the MCF-7 breast cancer cell line by Gandola *et al*.[129]. Considering these issues in addition to human trials, their actual biological effects must be studied in carefully through-out animal models[131]. Numerous studies have demonstrated the biological safety concern with phytophospholipid complexes in this area[71]. Additionally, rather than

using only pure phytoconstituents to demonstrate the superiority of a phytosomes, pharmacokinetic and pharmacodynamic specifics must be evaluated in animals and individuals. Another phase in the marketing process is determining the appropriate dosage form for improving absorption as well as the effectiveness of the finished product[133,134]. The manufacture of phytosomes on a big scale presents another difficulty. The product's qualities should be preserved, nonetheless, when scaling up. This has to do with how useful laboratory protocol is in an industrial setting[132,133]. Although the manufacturing procedures for many kinds of phytosomes are frequently easy, the low physicochemical stability of pH-sensitive phytosomes makes their industrial manufacture difficult[131]. Similar to other pharmaceutical goods, phytosomes should be repeatable and their quality should be monitored over time. Another aspect of the effective commercialization of a product is its popularity. With this, biocompatibility, affordability and the safety of plant-based products have increased people's desire for this sort of treatment in recent years. Additionally, because manufacturing phytosomes is advancing the technology to an industrial scale is simple, commercialization of phytosomes proceeds quickly[135]. Table 3, highlights the commercial phytosomes products available in market[136-141].

TABLE 3: COMMERCIAL PRODUCTS OF PHYTOSOMES [13,15,19,136-141]

S. no	Phytosomes	Phytoconstituents complex	Functions
1	Bilberry (melrtoselect) phytosome	Anthocyanosides from *Vaccinium myritillus*	Antioxidant, improvement of capillary tone
2	*Centella* phytosome	Terpenes obtained from *Centellaasitica*	Brain tonic, vain, and skin disorder
3	*Cucurbita* phyto-someTM	Tocopherols, steroids, carotenoids from *Cucurbita pepo*	Anti-inflammatory, benign prostatic hyperplasia
4	Curcumin (meri noselect)	Polyphenols contained in *Curcuma longa*	Enhancing plasma and oral bioavailability of curcuminoids as a cancer chemopreventive drug
5	*Echinacea* phytosome	Echinacosides derived from *Echinacea augustifolia*	Nutraceutical, immunomodulator
6	*Ginkgo biloba* dimeric flavonoids phytosome	Dimeric flavonoids extracted from *Ginkgo biloba* leaf	Lipolytic and vasokinetic agent
7	*Ginkgo biloba* terpenes phytosomes	Ginkgolides and bilobalide deriving out of *Ginkgo biloba* leaf	Soothing agent
8	*Ginkgo* phytosome™	*Ginkgo* flavonoids from *Ginkgo biloba*	Protects the brain and vascular linings, and acts as an anti-skin aging agent
9	*Ginkgoselect*®	The *ginkgo flavono* glycosides contained in *Ginkgo biloba*	Protection against brain and vascular lining
10	Ginseng phytosome™	Ginsenosides deriving out of *Panax ginseng*	Nutraceutical, immunomodulator
11	*Glycyrrhiza*	18-beta glycyrrhetinic acid	Anti-inflammatory activity
12	*Glycyrrhiza* phyto-some	Glycyrrhetinic acid deriving out of *Glycyrrhiza glabra*	Anti-inflammatory, soothing
13	Grape seed leucoselect)	Procyanidins from *Vitis vinifera*	Antioxidant and anticancer activity
14	Grape seed phytosome™	Procyanidins got from *Vitis vinifera*	Nutraceutical, systemic antioxidant, cardioprotective
15	Green tea Phyto-some™	Epigallocatechin obtained from *Thea sinensis*	Nutraceutical, systemic antioxidant, anticancer

16	Greenselect®	Epigallocatechin 3-O-gallate derived from *Camellia sinensis* (green tea)	Systemic antioxidants, protection against cancer and risk of cholesterol
17	Hawthorn phytosome™	Flavonoids derived from *Crataegus oxyacantha*	Nutraceutical, cardioprotective, antihypertensive
18	Madeglucyl phytosome™	Tannins from *Syzygium cumini*	Anti-hyperglycemic, anti-inflammatory, antioxidant
19	Melilotus (lymphaselect) phytosome	Triterpenes extracted from *Melilotus officinalis*	Hypotensive, indicated in insomnia
20	Olea select phytosome™	Polyphenol from *Olea europea*	Anti-hyperlipidemic, anti-inflammatory
21	Olive oil phytosome	Polyphenols gained from *Olea europaea* oil	Antioxidant, anti-inflammatory, antihyperlipidemic
22	PA 2 phytosome	Proanthocyanidin A2 from horse chestnut bark	Anti-wrinkle, UV protectant
23	Sabaselect®	through supercritical CO_2 (Carbon dioxide) extraction, a saw palmetto berry extract was produced	It is advantageous to the prostate's healthy functioning
24	Sericoside phytosome	Sericoside extracted from *Terminalia sericea* bark root	Anti-wrinkles
25	Silybin phytosome™	Silybin obtained from *Silybum marianum*	Hepatoprotective, antioxidant for liver and skin
26	Silymarin phytosome	Silymarin derived through milk thistle seed	Antihepatotoxic activity
27	Soyaselect phytosome™	Genistein and daidzein from *Glycine max*	Antiangiogenic, anticancer, cardio-protective, immunostimulatory, and hypocholesterolemic
28	*Swertia* phytosome™	Xanthones from *Swertia alternifolia*	Antidiabetic
29	Virtiva®	Ginkgoflavonglucosides, ginkgolides, bilobalide derived from *Ginkgo biloba* leaf	Vasokinetic
30	Visnadine (visnadax) phytosome	Visnadine from *Ammi visnaga*	Circulation improver, vasokinetic
31	ximifene and xime-noil phytosome™	Ximenynic acid, ethyl ximenynate from *Santalum album*	Improve microcirculation
32	Zanthalene	Zanthalene which is obtained from *Zanthoxylum bungeanum*	Anti-itching agent soothing agent and shows anti-irritant property

Recent trends on phytosomes to overcome its limitations:

Phytosome technology has shown significant promise in enhancing the bioavailability of phytoconstituents, it does come with certain limitations. These include the relatively high cost of production, the need for further research to fully understand the long-term safety and efficacy of phytosomes, and the challenge of scaling up the production process. However, ongoing research is actively addressing these limitations.

Reducing production costs: One of the primary limitations of phytosome technology is the high cost of production. This is due to the complexity of the process and the cost of the raw materials, particularly the phospholipids. Recent research is focused on finding more cost-effective methods of production and cheaper alternatives to phospholipids that can still form effective phytosomes. For instance, researchers are exploring the use of different types of lipids and surfactants that could potentially lower the cost of production[41].

Long-term safety and efficacy: While phytosomes have been shown to enhance the bioavailability of phytoconstituents, more research is needed to fully understand their long-term safety and efficacy. Clinical trials are being conducted to gather more data on the safety and efficacy of phytosomes over extended periods of use. These trials will provide valuable information that can guide the safe and effective use of phytosomes in drug delivery.

Scaling up production: Scaling up the production of phytosomes from the laboratory to industrial scale is a significant challenge. However, researchers are developing new methods and technologies to facilitate large-scale production. This includes the use of continuous flow reactors and other advanced manufacturing techniques that can increase production efficiency and reduce costs[1,41].

Broadening the range of phytoconstituents: While phytosome technology has been shown to enhance the bioavailability of a wide range of phytoconstituents, it may not be suitable for all phytoconstituents. Research is ongoing to identify which phytoconstituents can benefit from phytosome technology and to optimize the process for each specific phytoconstituent. Herbal extracts and phytochemicals with considerable therapeutic potential, such as curcumin, *Ginkgo biloba*, grape seed, silymarin and many more, are found in many products on the market based on phytosome technology[41] details of commercial products of phytosomes are tabulated in Table 3.

CONCLUSION

Because of amazing entrapment capability, biocompatibility, and safety, vesicles are demonstrated to be very promising cellular delivery platforms for a variety of beneficial phytochemicals. Phytosomes are vesicular drug carriers that form a complex between phytochemicals and phospholipids to improve the bioavailability and absorption of bioactive molecules while also enhancing the stability of the compound. An overview of the biological functions of phytosomes for both commercial and non-commercial products is covered in this paper. The collection of studies reveals a general benefit in using these formulations to increase the bioavailability of bioactive phytochemicals, allowing a dosage reduction or higher biological activity when compared to non-formulated compounds. Despite having numerous applications phytosomes have some limitations like leaching of the phytoconstituents from phytosomes which may diminish the target drug concentration and also indicates their unstable nature, manufacturing-related restrictions, and commercial challenges. So, researchers should address these issues in near future.

FUTURE SCOPE:

The extensive literature review reveals the many phytosome products and shows how they differ from traditional plant extracts in terms of their considerable medicinal and health-promoting characteristics. Plant extracts in their raw, partially purified, or fractionated forms can be standardized, then created as phytosomes for further research to reveal any prospective improvements. To create stimulator activity, future studies might combine phytosomes with a variety of other phytochemicals or combine medications and phytochemicals in a single nano-vesicle. In terms of skin permeability and stability, phytosomes are identical to liposomes.

However, in phytosomes, the polar head of the phospholipid forms a Hydrogen bond (H-bond) with the polar properties of the bioactive molecules, allowing it to interact with the phytochemicals. This considerably increases the stability and skin penetration of phytochemicals in comparison to liposomes. Even though clinical trials are currently insufficient to assess the bioactivities of certain compositions, the conclusive evidence in favor of these compositions is encouraging, and specialists are urged to carry on their research in this area. Phytosomes can be created in the future for a variety of therapeutic uses, including hepatoprotection, cardiovascular disorders, liver illnesses, anti-inflammatory, immunomodulator, anti-cancer, anti-diabetes, as well as prophylactic and health purposes as nutraceuticals. Interest in these developments will be sparked by clinical trials on standardized products that show better efficacy compared to non-formulated components or extracts. The promise of this formulation strategy to address the issues associated with phytochemicals for their successful transdermal administration for local and systemic action is demonstrated by all current research efforts for the phytochemical loaded lipid in vesicle transferosomes. Additional clinical study results

of such a drug delivery platform will soon reveal its possible future applications.

Conflict of interests:

The authors declared no conflict of interests.

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