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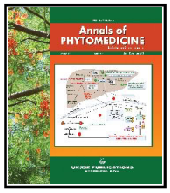

Review Article : Open Access

A comprehensive review on phytosomes as a novel dosage form for herbal medicines

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Abstract

Nowadays, natural remedies are used to treat the majority of prevalent diseases and nutritional issues. Any herbal medication's efficacy depends on the therapeutically active compound being delivered at an effective dosage. Some phytoconstituents like polyphenolic and flavonoid compounds in the herbal medicines are hydrophilic in nature and bigger molecular size. Due to their low lipid solubility and bigger molecular size, a higher dose is needed for therapeutic effect. To solve these difficulties, newly introduced novel dosage form phytosomes, helps to increase effectiveness of herbal medicines. The name phytosomes indicated "cell-like". It is mainly prepared by suspending phospholipid and phytoconstituents/extract in an appropriate solvent. Phytosome technology has been successfully applied to increase the bioavailability, efficacy and nutrition values of numerous well known herbal extracts such as *Silybum marianum*, *Ginkgo biloba, Vitis vinifera, Camellia sinensis, Centella asiatica, Santalum album, Olea europaea and Panax ginseng*. This compilation highlighted the methods of preparations, advantages/disadvantages and ccharacterization including complex formation efficiency, particle size analysis, particle surface morphology, surface charge, and molecular interactions of phytosomes. Several cost-effective phytosomes are available in the market, including Ginkoselectβ®, Siliphosβ®, Greenselectβ®, Leucoselectβ®, Sabalselectβ®, Centevitaβ®, and Soyselectβ®. This review also discusses several antidiabetic phytosomes and their potential molecular mechanisms, such as restoring the size of pancreatic islets and maintaining β cells, inducing insulin secretion from β cells, improving glucose tolerance, decreasing gluconeogenesis, promoting glucose uptake and consumption in the skeletal muscle and liver *via* accelerating the levels of the enzymes hexokinase-2, peroxisome proliferator-activated receptor, and glucose transporter type 4.

1. Introduction

The use of herbs has been employed since ancient times for the cure and prevention of many diseases. The faith that natural drugs are significantly safer than synthetic medications has gained success in recent years, which has resulted in utilization of phytopharmaceuticals is increasing and formulations of phytomedicines are developing. It has been investigated to provide a wide range of dose formulations for herbal medications (Pathan *et al.,* 2011).

Phytoconstituents derived from plants have been used to cure a variety of ailments (Saller *et al.,* 2001). Silybin derived from milk thistle fruit throughout almost 2000 years has been utilized to nourish the liver (Celik *et al.,* 2015; Islam *et al.,* 2021). Curcumins, which are derived from turmeric, have been shown to have antioxidant and anticancer activities (Namratha *et al.,* 2013; Ramsewak *et al.,* 2000). Furthermore, polyphenols, such as terpenoids, phenolic compounds, and flavonoids are among the most extensively researched active ingredients (Apostolova *et al.,* 2015; Dai *et al.,* 2010). These compounds have caught the interest of scientists worldwide due to their powerful bioactivity against many diseases, minimal cytotoxicity, and capacity to be used in the manufacturing of cosmetics and dietary supplements (Oveissi *et al.,* 2019; Kooti *et al.,* 2017). However, many of these plant-based active substances are poorly absorbed when consumed orally, preventing their widespread application (Teng *et al.,* 2012; Manach *et al.,* 2004). Phytoconstituents like polyphenolic and flavonoid compounds in the herbal medicines are hydrophilic in nature and bigger molecular size. Due to their low lipid solubility, which restricts their capacity to pass through the enterocytes' lipid-rich outer membranes, these types of molecules are poorly absorbed when administered orally and topically, resulting in poor bioavailability and negligible efficiency. As a result, a higher dose needs to be used for dosage delivery (Kidd *et al.,* 2008; Yang *et al.,* 2009). To solve such problems, the novel drug delivery technology improves the efficacy of herbal medicines while reducing their side effects. Phytosomes are newly introduced patented technology of novel dosage form that is involves interaction between phospholipid and water-soluble phytoconstituents shown in Figure 1 in order to increase the bioavailability and therapeutic impact of the herbal

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medication, which is suitable for the oral and topical drug delivery systems (Thakur *et al.,* 2021; Bombardelli *et al.,* 1991; Bombardelli *et al.,* 1991).

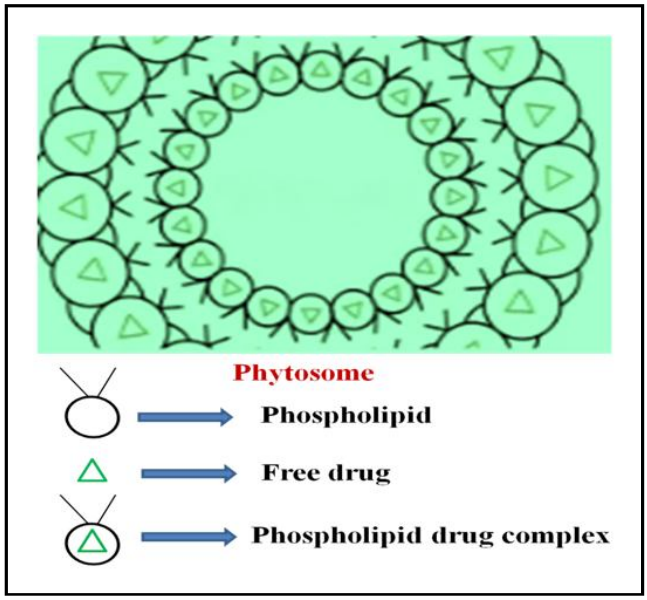

Figure 1: A structure of phytosomes.

1.1 Phytosomes

The phytosome, also known as the phytolipids delivery system, serves as a link between conventional and novel methods of drug delivery. It is a recently launched patented method created by Indena. To create lipid compatible molecular complexes, standardized plant extracts or water soluble phytoconstituents are incorporated into phospholipid that increases absorption and bioavailability (Bhattacharya *et al.,* 2009). The name "phyto" refers to a plant, while "some" refers to a cell-like structure, which is sometimes referred to as a herbosome in the literature. When different plant-derived compounds like flavonoids, terpenes, and saponins form reversible complexes with phospholipids, their anti-inflammatory and vasokinetic actions are elevated and longer lasting than when the same quantity of material is administered in its natural state. This is mostly due to the active ingredient complexation with phospholipids (Jain *et al.,* 2010; Choubey *et al.,* 2011).

Phytosome technology has emerged as a dedicated and promising approach for novel drug delivery, with enhanced efficacy, quality, and targetability of active plant constituents. As reported by Kumar *et al.* (2020), phytosomes exhibit better metabolic profiles than conventional herbal extracts. Although, natural plant active components have been shown to possess strong *in vitro* pharmacological activities, their *in vivo* absorption is often limited. To overcome the drawbacks and negative effects associated with traditional herbal extracts, phytosomes have been developed as an emerging nanotechnology that can improve the miscibility of bioactive phytoconstituents in lipid-rich barriers, thereby enhancing their bioavailability and absorption. Among various novel drug delivery systems (NDDS), phytosomes are well known biocompatible nanocarriers that can be used to increase the solubility and permeability of phytopharmaceuticals. Therefore, many novel drug delivery carriers are being employed for targeted delivery of phytoconstituents at the site of action, making phytosomes a growing and promising technology for drug delivery (Gaikwad *et al.,* 2023).

Because the phytosomes procedure generates a small cell, the herbal extract's therapeutic components are shielded from degradation by secretions from the digestive system and bacteria in the gut. Phytosomes are better able to move from an environment that is hydrophilic to the environment of the enterocyte cell membrane that is lipid friendly, and then in side the cell and eventually into the blood (Manach *et al.,* 2004).

1.2 Phytosome technology

Flavonoids and terpenoids, which are constituents of plant extracts that are water soluble, have the affinity to bond with phospholipid (phosphatidylcholine) directly. In a non-polar solvent, standard extract and phosphatidylcholine are allowed to react in a stoichiometric proportion. A bifunctional molecule called phosphatidylcholine, which has a hydrophilic choline moiety and a lipophilic phosphatidyl moiety, assists in increasing the water-soluble phytoconstituents' bioavailability. The choline group, which is hydrophilic, binds to water-soluble phytoconstituents to create the body, while the phosphatidyl group, which is lipid-soluble, produces the tail and encircles the choline-bound material. The result is a molecular structure known as a phytosome is created that is lipid compatible. Specific spectroscopy techniques can reveal that the molecules are connected to the polar choline portion of phosphatidylcholine through chemical interactions (Bombardelli *et al.,* 2009; Bombardelli *et al.,* 1994). Solvent, ratio of the active chemical compounds and phospholipid, reaction temperature and reaction time are the main factors that determine the development of phytophospholipid complexes (Saoji *et al.,* 2016).

Various techniques have been posited for the preparation of phytosomes, including the rotary evaporator method, antisolvent precipitation technique, freeze drying cosolvency, reverse phase solvent method, thin film hydration and ethanol injection method, and salting out technique. The evaporator approach and solvent evaporation are widely employed methods for producing phospholipid complexes, as evidenced by their popularity and common usage (Barani *et al.,* 2021; Kumar *et al.,* 2023; Talaat *et al.,* 2023).

1.3 Components of phytosomes

1.3.1 Phospholipids

Egg yolk and plant seeds are very rich in phospholipids. Industrially manufactured phospholipids are presently available (Ghanbarzadeh *et al.,* 2016). Phospholipids may be categorized as glycerophospholipids and sphingomyelins. Phosphatidylcholine (PC), phosphatidic acid (PA), phosphatidylethanolamine (PE), phosphatidylserine (PS) and phosphatidyl glycerol (PG) are main examples of glycerophospholipids. The most common phospholipids utilized for forming phytosomes comprising two hydrophobic hydrocarbon chains and a hydrophilic head group (Li *et al.,* 2015). Phosphatidylcholine (Figure 2) is the most widely used phospholipid in the formulation of phospholipid complexes.

PC has amphipathic characteristics that allow it to be moderately soluble in aqueous and lipid environments. In addition PC is a fundamental component of cell membranes. It is a biocompatible

and nontoxic. PC molecules have been found to have hepatoprotective characteristics as well as therapeutic effects in the treatment of liver disease such as hepatitis, fatty liver, and hepatocirrhosis (Suriyakala *et al.,* 2014; Duric *et al.,* 2012). High affinity siramesine and PA small molecule phospholipid complexes were produced in a study (Patel *et al.,* 2009).

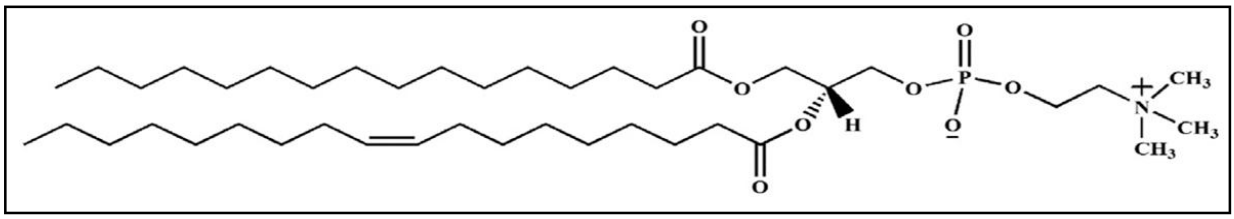

Figure 2: Chemical structure of phosphatidylcholine.

1.3.2 Phytoactive constituents

Researchers often characterize the active components of herbal extracts based on their significant pharmacological effects observed *in vitro* rather than *in vivo* activities. These components predominantly consist of polyphenols, with hesperidin being one such biologically active polyphenolic compound found in plants. These polyphenols tend to favor the aqueous phase and have limited ability to penetrate biological membranes. Phytophospholipid complexes play a crucial role in enhancing the solubility of lipophilic polyphenols in the aqueous phase and improving the membrane-penetrating capabilities of hydrophilic polyphenols. Additionally, complex formation can provide protection to polyphenols against external factors such as hydrolysis, photolysis, and oxidation, among others (Kidd *et al.,* 2008). Moreover, various compounds like evodiamine and siramesine, derived from herbal extracts, can also form complexes with phospholipids, in addition to polyphenols (Tan *et al.,* 2012; Parry *et al.,* 2008). Consequently, it is important to note that the process of producing phytophospholipid complexes is not limited to polyphenols alone; potentially, any active chemical may utilize this complexation process.

1.3.3 Solvents

Various solvents have been utilized in different studies as the reaction medium when developing phytophospholipid complexes. Protic solvents as ethanol effectively taken the role of aprotic solvents, which were previously utilized to create phytophospholipid complexes. Examples of aprotic solvents include cyclic ethers, methylene chloride, halogen derivatives, aromatic hydrocarbons, or ethyl acetate (Khan *et al.,* 2012).

1.3.4 Stoichiometric ratio of phytoconstituents and phospholipids

Typically, phytophospholipid complexes were made by reacting an artificial or biological phospholipid with the active components at a molar ratio between 0.5 and 2.0 (Tripathy *et al.,* 2013). A stoichiometric ratio of 1:1, on the other hand, is thought to be the most effective ratio for forming phospholipid complexes (Chauhan *et al.,* 2009). Various stoichiometric ratios of phytoconstituents and phospholipids, however, have been used. Yue *et al.* (2009). performed a comparative investigation using the stoichiometric ratios of 1:1, 1.4:1, 2:1, 2.6:1, and 3:1 to create oxymatrine-phospholipid complexes; he discovered that a ratio of 3:1 yielded the greatest amount Yue *et al.* (2009).

1.4 Properties of phytosomes

The physicochemical and biological characteristics of phytosomes were given (Kumar *et al.,* 2017; Bhattacharya *et al.,* 2009; Bhattacharya *et al.,* 2009; Prasad *et al.,* 2016; Marena *et al.,* 1991).

1.4.1 Physicochemical properties

- Phytosomes are a complex formed by combining phytoconstituents or plant extract with natural or synthetic phospholipids. The complex is formed by reacting an adequate amount of phospholipid and phytochemicals or plant extract in an appropriate solvent.
- The association between the phospholipid and the substrate is caused by hydrogen bond forming between the phospholipid's polar head and the polar functions of the principal components.
- When immersed in water, phytosomes assume a micellar shape, developing liposomal similar structures.
- Phytosomes are freely soluble in non polar solvents, form micelles in polar solvents (water), and have intermediate fat solubility.
- Phytosomes have a distinct melting point.
- The phytosomes ranges in size from 50 nm to a few hundred m.

1.4.2 Biological properties

- When taken orally, phytosomes enhance the active absorption of active molecules as well as the systemic absorption.
- They are herbal products in their most advanced form, and they are more effective than classical herbal extracts.
- Phytosomes pharmacokinetics is superior to those of conventional herbal medicines.

1.5 Advantages of phytosomes

(Dayan *et al.,* 2002; Facino *et al.,* 2014; Semalty *et al.,* 2006; Amin *et al.,* 2012)

- It increases the absorption of polar phytoconstituents that are lipid insoluble through oral and topical routes, demonstrating improved bioavailability, leading to a markedly increased therapeutic effect.
- The amount of active ingredient(s) required is reduced as a result of higher absorption.
- High bioavailability results in minimized dose required.
- Phosphatidylcholine, a carrier for phytoconstituents involved in the development of phytosomes, also exhibits hepatoprotective properties.
- The transdermal absorption of phytoconstituents when applied in the form of phytosome is improved, and they serve as a functional beauty.

- Greater clinical benefits.
- They permeate the botanical extract that is non-lipophillic is absorbed better in the intestinal lumen.
- Since phytosomes were readily accessible, they were employed to deliver flavonoids that protect the liver.
- The phytosomes are more stable profiles than liposomes because phosphatidylcholine molecules and phytoconstituents develop chemical bonds.
- The phospholipid coating on the water-soluble phytoconstituents shields them from digestion by gut bacteria and digestive enzymes. It assists in drug delivery to the targeted tissue.

1.6 Disadvantages (Saha *et al.*, 2013; Bhattacharya *et al.*, 2009)

There are a few drawbacks of phytosomes. For example, phospholipids (lecithin) can stimulate the proliferation of MCF-7 breast cancer cell lines, and it has been reported that phytosomes can rapidly eliminate phytoconstituents.

2. Method of phytosomes preparation

Mostly for the preparation of phytosomes or phytophospholipid complexes two processes are used; namely, solvent evaporation and anti-solvent precipitation method. Solvent evaporation is a conventional and regularly used method for the preparation of phytosomes. Phytosomes of leaves extract of *Bombax* were prepared by solvent evaporation technique. The phospholipid (Soya lecithin) and phytoconstituents/extract are suspended in the appropriate solvent for this method, and the mixture is refluxed for a few hours. Under vacuum, the resulting clear mixture evaporates (Karole *et al.,* 2019).

Antisolvent precipitation process was applied for the preparation of sinigrin-phytosome complex by using organic solvents as a reaction media. Initially, solvent evaporation method was used, where the sinigrin and phosphatidylcholine were retained in a dichlromethane solvent. The reaction was allowed to proceed for a short period of time until the dichlromethane was completely evaporated. Then, the anti-solvent approach was used to separate the sinigrin-phytosome complex from the organic solvent by using n-hexane as the anti-solvent (Mazumder *et al.,* 2016).

Other method for preparing phytosomes is anhydrous co-solvent lyophilization. This approach was used to create the kaempferol-phospholipid complex (KPLC). Briefly, kaempferol and phospholipon were precisely weighed and put into a 100 ml round-bottom flask. Both components were dissolved in 20 ml of 1, 4-dioxane and refluxed. The reflux reactions were conducted using a water bath for a two-hour period at 40°C, 50°C, and 60°C. The reaction mixture was freeze-dried with a lyophilizer after two hours (Darshan *et al.,* 2016).

Several strategies presented in various studies are discussed here. The supercritical anti-solvent precipitation method was used to make puerarin phospholipids complexes and argued that supercritical fluids were more accurate to traditional procedures for the creation of medicinal phospholipids complexes (Li *et al.,* 2008). The salting-out method and the film production approach were used to synthesized phytophospholipids complexes (Damle *et al.,* 2016).

3. Characterization of phytosomes

3.1 Solubility and partition coefficient

For characterization of active ingredients or active constituent in phytophospholipids complexes or in physical mixtures, it is necessary to determine the solubility in water or organic solvents, as well as the n-octanol/water partition coefficient (P). In comparison to active components, phytophospholipid complexes often have higher hydrophilicity and lipophilicity values. A study was established that complex embelin was more soluble in n-octanol and water than embelin and its specific physical mixtures (Pathan *et al.,* 2012).

3.2 Complex formation efficiency

Complex formation efficiency is also called as drug entrapment/ encapsulation/entrapment efficiency. This is a critical feature of the finished complex since it affects the validity of the preparation process as well as the various preparation parameters and variables. The two major approaches for determining the complex formation efficiency are direct and indirect methods. Both approaches use centrifugation to separate the complexes from the uncomplexed elements in the medium, and UV spectrophotometry to quantify them (Sikarwar *et al.,* 2008; Keerthi *et al.,* 2014) or by HPLC (Jena *et al.,* 2014). The % entrapment efficiency was determined using the equation given below:

Entrapment efficiency (%) = (Entrapped drug)/(Total drug) × 100

Mazumder has assesed Complex efficiency (%) 69.5 ± 5 for sinigrin-phytosome complex, there is no notable change in complex efficiency over a three-month time frame. (Mazumder *et al.,* 2016).

3.3 Particle characterization (particle size and distribution)

The size distribution and mean size of phytosomes are crucial criteria that influence the product's overall performance. Particle size, size distribution, and solid surface interactions all have varying degrees of influence on drug dissolution rate, absorption rate, dosage form content uniformity, and stability. There are several ways for determining particle size, but the two most common ways are dynamic light scattering (DLS) and scanning electron microscopy. The DLS is the primarily used technique for this purpose since it is a widely accepted, non-invasive tool for measuring the size and size distribution of molecules and particles in the submicron region (Malvern *et al.,* 2004). The normal particle size of phospholipid complexes varied from 50 nm to 100 µm. Dhase produced phytosomes of methanolic extract of leaves of *Aegle marmelos,* the average particle size was found 212.6 nm (Dhase *et al.,* 2015).

3.4 Particle surface morphology

Transmission electron microscopy (TEM) or scanning electron microscopy (SEM) can be used to examine the phytosome. These techniques may be used to investigate the surface order of complexes. The *Mangkokan* leaf extract was formulated into phytosome, which was appeared as irregular spherical vesicles structure (Rahmi *et al.,* 2021).

3.5 Surface charge

Zeta potential defines the charge of phytosomes in emulsions. The magnitude of the zeta potential is a sign of the phytosomes' potential stability. By running an electrophoresis experiment on the sample and using laser doppler velocimetry to calculate the electrophoretic

mobility, (-20.6mV to -26.4mV) (Saini *et al.,* 2013). A stable phytosome has a zeta potential more than 30 mV or less than -30 mV (Dhase *et al.,* 2015).

3.6 Analysis of molecular interactions and complexation between phytophospholipid complexes

A confirmatory analysis is used to verify Molecular interactions and complexation between phytoconstituents and phospholipids during phytosome characterization. Techniques such as ultraviolet spectroscopy (UV-spectra), differential scanning calorimetry (DSC), Fourier transform infrared spectroscopy (FTIR), X-ray diffraction, and nuclear magnetic resonance (NMR) were employed and are briefly discussed.

3.6.1 Ultraviolet spectra (UV-spectra)

UV absorption patterns in samples can be utilized to characterize their structural properties. A large number of studies have revealed no differences in UV absorption characteristics of components before and after complexation. When luteolin-phospholipid complexes were created, which were showed luteolin's distinctive peak (Xu *et al.,* 2009).

3.6.2 Fourier transforms infrared spectroscopy (FTIR)

FTIR is an important technique for analysis of molecular interactions and complexation between the phytoconstituents and phospholipids. It is feasible to confirm the structural analysis and formation of phytophospholipid complexes by matching the spectroscopy of phospholipid complexes with those of physical mixtures. Different studies may yield different findings. The FTIR spectroscopy of phytosomes of *Aegle marmelos* leaves revealed the development of strong hydrogen bonds between phospholipon hydroxyl group and extract phytoconstituents (Dhase *et al.,* 2015). The piperine (extracted from *Piper nigrum*) phytosomes with domperidone consisting of phosphatidylcholine was synthesized. The molecular interactions between domperidone, phosphatidylcholine, and piperine were investigated by FTIR studies. The detailed examination of each characteristic peak and its matching wave number revealed that there was no significant interaction between the excipients and the domperidone. However, trapping within the vesicles was likely to blame for the attenuation of the domperidone characteristic peak intensity (Islam *et al.,* 2021). FTIR spectra of *Moringa oleifera* leaf extract phytosomes consist of extract, phospholipids was revealed a molecular interaction. The phytosomes spectra revealed a dramatically lowered intensity and shifting of the-O-H peak at 3354 cm^{-1} as well as the appearance of a new peak N-H stretching groups of amines at 1600 cm^{-1}. These interactions could be caused by ionic bonds or Van der Waals forces. The bonds created between the extract's OH groups and the amine phosphate groups of phospholipids (Wardana *et al.,* 2022). When the FTIR spectrum of phytosomes (bitter melon extract) was compared to the spectrum of chemical constituents of bitter melon extract and phosphatidylcholine, it was discovered that there was a hydrogen link between phosphatidylcholine and phytoconstituents (Sasongko *et al.,* 2019). The phytosomes of leaves extract of *Bombax ceiba* was prepared by solvent evaporation technique. When the extract and polymer mixture was tested for physicochemical compatibility using a Fourier Transform Infrared Spectrophotometer, no peaks appeared or vanished, indicating that there was no chemical connection between the extract and lipid (Karole *et al.,* 2019).

The phytosome of stem extract of *Tinospora cordifolia* was developed by utilizing thin film hydration method. The compatibility of pure fraction and the physical mixture of fraction with soya lecithin and phytosome formulation was investigated using FTIR spectroscopy. The FTIR spectra revealed that the drug's distinctive peak was also present in the combination. The functional groups are within the limit, and there is no drug-excipient interaction (Thakur *et al.,* 2021). The phytosomes with Vasaka were prepared and intermolecular interaction of optimized phytosome was characterized by studying the FTIR spectral analysis. As a result of the interaction with phospholipids, the FTIR spectra of alkaloid extracts showed alterations in specific positions. The variation between the stretching patterns of phenolic OH in phytosome of alkaloid extracts suggested that weak intermolecular interactions between phospholipids and extracts were responsible for phytosome formation (Nandhini *et al.,* 2021).

3.6.3 X-ray diffraction

X-ray diffraction is a useful technique for studying the microstructure of both crystal and amorphous materials. Active constituents or active constituent phytophospholipid complexes, phosphatidylcholine and their physical combinations are widely subjected to X-ray diffraction. The crystalline behaviour of Vasaka-loaded phytosomes revealed that the phytosome's diffraction pattern showed intense and sharp crystalline peaks. The crystallinity of the optimized phytosome was found that extract might be molecularly spread out within the phospholipid matrix and exists in an amorphous shape (Nandhini *et al.,* 2021). To determine the substance's crystallinity, an XRD study involving pure extract, PC, and *Aegle marmelos* phytosome was done. In contrast to phospholipid, which revealed an amorphous status devoid of a crystalline peak, extract's powder diffraction pattern showed strong crystalline peak/maxima. Crystalline maxima of extract had vanished from the complex (Dhase *et al.,* 2015).

3.6.4 Differential scanning calorimetry (DSC)

To characterize a solid phytosome, the technique of differential scanning calorimetry (DSC) is used to detect and analyse thermal events such fusion, solid-solid transitions, glass transitions, loss of solvent, and a breakdown. In DSC, interactions can be detected by measuring the transition temperature, the emergence of new peaks, the disappearance of previous peaks, melting points, and alterations in the relative peak area (Hao *et al.,* 2013). DSC thermogram of phosphatidylcholine (PC) showed an endothermic peak, Rutin (RN) showed broad endothermic peak. Endothermic peak was seen in the physical mixture of PC and Rutin, which was almost 1ºC lower than the single compounds. The DSC thermogram revealed two distinctive peaks which were smaller than those of the physical mixture as well as the rutin and PC peaks vanished. The complexes' phase transition temperature was lower than PC's phase transition temperature. The thermogram indicated that PC and RN may have interacted in some way (Das *et al.,* 2015). Such interaction resulted from union of hydrogen bonds or van der Waals forces, however it did not result in the generation of a new compound (Xu *et al.,* 2009).

3.6.5 Nuclear magnetic resonance (NMR)

The ^{1}H NMR and ^{13}C NMR approaches have been extensively utilised to identify the complexes' structural features. According to NMR studies, the polar phenolic functional groups of silybin and the

phospholipids can establish hydrogen bonds. The spectra of several phytophospholipid complexes suggest that the central choline-bioactive components of these complexes may serve as an envelope covered by the hydrophobic side of lipids (Angelico *et al.,* 2014).

4. Commercially available phytosome products

Some successful products of phytosomes that are commercially available in the market (Table 1).

Table 1: Commercially available phytosomes with their company/trade names and uses

S. No.	Sources	Phytoconstituents	Trade/Common names	Company names	Uses	References
1	*Gingko biloba*	Dimeric flavonoids18, terpenoids (gikgolides and bilobalide)	Ginkoselectβ® phytosome	Herbal factors lining	Antiageing and brain vascular	Naik *et al.,* 2006
2	*Silybum marianum*	Silybin, silymarin	Siliphosβ®	Indena	Antioxidant and hepatoproptective	Kidd *et al.,* 2005; Tedesco *et al.,* 2003
3	*Crataegus oxyacantha*	Flavonoids	Hawthorne phytosomes	Indena	Antioxidant, cardioprotective	Suryawanshi *et al.,* 2011
4	*Camellia sinensis*	Catechins and their gallate derivatives	Greenselectβ® phytosome	Indena	Antioxidant, anticancer	Di Pierro *et al.,* 2009; Gilardini *et al.,* 2016
5	*Terminalia serica*	Sericosides	Sericosides phytosome	-	Skin restructuring, capillary protecting, anti-inflammatory	Franceschi *et al.,* 2007
6	*Panax ginseng*	Ginsenosides	Ginseng phytosome™	Natural factors	Nutraceutical, immunomodulator	Kiefer *et al.,* 2003
7	*Vitis vinifera*	Procyanidine	Leucoselectβ® Grape seed phytosome	Indena	Cardio-protectant, antioxidant.	Magrone *et al.,* 2014; Vigna *et al.,* 2003
8	*Serenoa repens*	Phytosterol	Sabalselect β® phytosome	Indena	Non-cancerous prostateenlargement.	Naik *et al.,* 2006
9	*Oleaeuropaea*	Verbacoside, tyrosol, hydroxytyrosol	Oleaselect™ phytosome	Indena	Anti-inflammatory and antihyperlipidemic	Shivanand *et al.,* 2010
10	*Echniacea angustifolia*	Echinacosides and highmolecular weight polysaccharide (inulin)	Echinacea phytosome™	Indena	Neutraceutical, immunomodulator	Sgorlon *et al.,* 2012
11	*Glycerrhyza glabra*	Glycerrhetinic acid	18 β-glycyrrhetinic acid phytosome	Indena	Soothing, Anti-inflammatory activity	Bombardelli *et al.,* 1989
12	*Centella asiatica*	Asiatic acid, madecassicacid	Centevitaβ®	Indena	For skin disorders, antiulcer, wound healing, hair falling	Sbrini *et al.,* 2020
13	*Citrus aurentium*	Naringenin	Naringenin phytosome	-	Anti-oxidant, Anti-inflammatory effect	Yu *et al.,* 2020
14	*Swertia alternifolia*	Xenthones 26	Xanthones phytosome	-	Anti-oxidant	Kalita *et al.,* 2013
15	*Serena repens*	Phytosterol	Sabaselect phytosome™	Indena	Non-cancerous prostate enlargement	Patil *et al.,* 2012
16	*Melilotus officinalis*	Melilotoside, terpenoids	Lymphoselect phytosome	Indena	Used for chronic venous insufficiency of the lower limbs	Albrigo *et al.,* 2019
17	*Santalum album*	Xemenynic acid, ethyl xemenynate	Ximiline and ximenoil	-	Improves microcirculation	Acharya *et al.,* 2011

18	*Vaccinum myrtellus*	Anthocyanoside	Mirtoselect phytosome™	Indena	Antioxidant, anti-inflammatory, diabetic retinopathy	Artaria *et al.,* 2007
19	*Aesculus hippoc astenum*	Saponins	Escin sitosterol phytosome™	Indena	Antiedema, vasoactive properties	Sunitha *et al.,* 2011
20	*Cucurbita pepo*	Tocopherol, carote-noids	Cucurbita phyto some/Tocopherol, carotenoids phytosome	-	Anti-inflammatory, prostatic hyperplasia	Huang *et al.,* 2020
21	*Glycine max extract*	-	Soyselect®/ soybean extract phytosome	Indena	Anti-angiogenic, anticancer, cardioprotective, immunostimulatory	El-Menshawe *et al.,* 2018
22	*Evodiamine*	-	Evodiamine pho-spholipids complex	-	Antitumor	Liu *et al.,* 2012
23	*Rhizoma paridis* from *Paris polyphylla*	Steroidal saponins	Rhizoma paridis phytosome	-	Antitumor activity, immunity adjustment, antiviral and anti-inflammation	Liu *et al.,* 2013

5. Antidiabetic phytosomes

Some successful antidiabetic phytosomes and their antidiabetic mechanism of action listed in Table 2 and Figure 3.

Table 2: Antidiabetic phytosomes with their phytoconstituents and mechanism of action

S. No.	Sources	Phytoconstituents	Part used	Possible mechanism	References
1	*Tinospora cordifolia*	Alkaloids, furanoditerpenoids, norditerpenoids, sesquiterpenoids, phenolics, lignin (epiyangambin), and sterols	Hydroalcoholic extract of *Tinospora cordifolia*	Decrease levels of lipid choles-terol, LDL, VLDL, and triglycerides	Deivasigamani *et al.,* 2023
2	Rutin	Quercetin glycoside	-	Restored the size of pancreatic islets and maintained the β cells	Rashmi *et al.,* 2016
3	*Momordica dioica*	Alkaloids, lectins, sitosterol, saponin glycosides, triterpenoids, saponins, long chain aliphatic hydrocarbons, tannins and fixed oil	MeOH extract of fruits	Hypoglycemic effect in STZ-NAD model	Sushila *et al.,* 2017
4	*Swertia chirata and Zizyphus mauritiana*	Catechins and theirgallate derivatives	Hydroalcoholic solution of leaves	Glucose tolerance test suggested that the phytosomes of both the extract prevented the increased blood glucose level	Anju *et al.,* 2023
5	Chrysin	Flavonoid	-	An oral glucose tolerance test and homeostatic model assess-ment for insulin resistance were significantly improved Suppressed gluconeogenesis *via* down regu-lation of phosphoenol pyruvate carboxykinase while it promoted glucose uptake in the skeletal muscle and liver Improved glucose utilization in the muscle was confirmed by upregulation of glucose transporter type 4, hexokinase2 and peroxisome proliferator-activated receptor Induced promotion of GLUT4 plasma translocation was con-firmed in the skeletal muscle	Seong-min *et al.,* 2020

6	*Syzygium cumini*	Alkaloid-jambosine, polyphenols -gallic acid, ellagic acid,	Hydro alcoholic extracts of seeds	Better and fast reduction of glucose in Oral glucose tolerance test	Amudha *et al.*, 2018
7	*Murraya koenigii*	Carbazole alkaloid, bioactive coumarins and acridine alkaloid. Additionally, it also contains phytochemicalssuch as girinimbin, iso-mahanimbin andkoenimbin.	Hydroalcoholic extract of leaves	Decline in glucose level in blood could be amplification of insulin effect by inducing either the insulin secretion from the remainder β-cells islets or its receptiveness	Anjna *et al.*, 2022
8	*Allium cepa*	Quercetin, kaempferol and oleanolic acid.	*Allium cepa* standard extract	Improving the glycemic control mechanisms and increasing insulin secretion from pancreatic β-cells	Prasanna *et al.*, 2022
9	*Citrullus colocynthis Momordica balsamina and Momordica dioica*	Alkaloids, flavonoids, saponins, tannins, carbohydrates, glycosides, colocynthin	Methanolic extracts of fruits	Oral glucose tolerance test showed remarkable control in the levels of Fasting Blood Glucose	Sushila *et al.*, 2018
10	Berberine	Isoquinolin alkaloid	-	The hypoglycemic effects were evidenced by the markedly declined fasting blood glucose levels (may enhance sensitivity toward insulin followed with stimu-lating glucose utilization)	Yu *et al.*, 2016
11	Curcumin	Curcuminoids	-	Improvement in fasting plasma insulin	Cicero *et al.*, 2020
12	*Citrus bergamia*	Naringin	Standardized extract	OGTT showed reduction of fasting plasma glucose	Mollace *et al.*, 2019

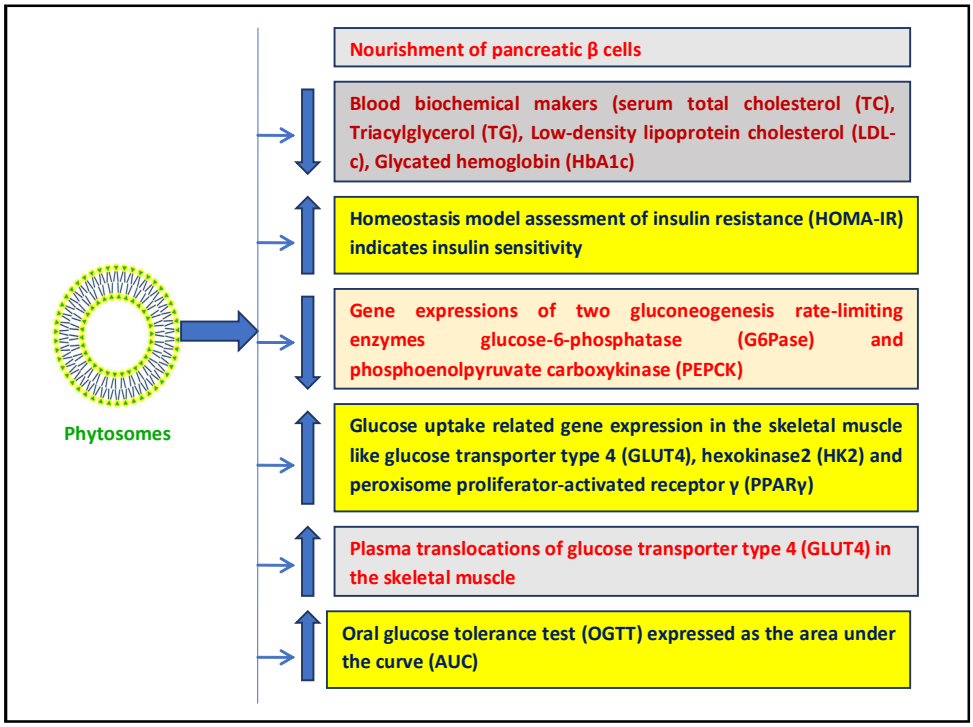

Figure 3: Phytosomes showing possible antidiabetic mechanism.

6. Conclusion

Phytosomes is one of the novel dosage forms of herbal medicines. Phytosomes are innovative formulations that increase the bioavailability of hydrophilic compounds with larger molecules, such as polyphenols and flavonoids. They are superior to other traditional formulations in many ways. The techniques employed in the production of phytosomes are straightforward and readily scalable for industrial purposes. It is common knowledge that the structural composition of phospholipid complexes can be effectively characterized and validated, thereby demonstrating the propensity for phospholipids to engage phytoconstituents through hydrogen bonding interactions. The possible application of phytophospholipid complexes has a promising future for utilization in the pharmaceutical industry with the support of clinicians and other researchers.

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Conflict of interest

The authors declare no conflicts of interest relevant to this article.

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