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PHYTOSOMES: INNOVATIVE DRUG DELIVERY SYSTEM FOR EFFECTIVELY DELIVERING BIOACTIVE PHYTOCONSTITUENTS AND PLANT EXTRACTS

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ABSTRACT

Herbal medications with a large concentration of active constituents have strong bioactivity *in vitro* but weak *in vivo* bioactivity owing to poor lipid solubility and molecule scale. As a result, the active components of the herbal extract are badly absorbed and bioavailable. A phyto-phospholipid complex vesicle (Phytosomes) is a promising modern strategy for increasing the bioavailability of herbal extracts and phytoconstituents in pharmaceuticals. Phytosomes are advanced herbal formulations that include the bioactive phytoconstituents of herbal extracts and have the capacity to move from a hydrophilic to a lipophilic state of the cell membrane, resulting in a stronger pharmacokinetic and pharmacodynamic profile than traditional herbal extracts. They can be made in a number of medication types, including suspensions, tablets, creams, and gels. This article discusses recent advances in phytosomes, as well as their use in different standardized herbal extracts, with the aim of providing comprehensive research on phytosomes as a promising drug delivery mechanism.

KEYWORDS: Phytosomes, Phyto-phospholipid complex, Phospholipids, Herbal Extract, Phytoconstituents, Drug Delivery.

1. INTRODUCTION

Plant active molecules from herbal extracts, which have historically been used in home remedies, are gradually being used in modern medicine.[1] Some phytoconstituents, on the other hand, have long side chains and strong polarity, preventing passive diffusion across lipidic skin.[2] The majority of phytoconstituents, such as flavanoids, terpenoids, and polyphenolics, have been shown to be strongly polar or water-soluble molecules.[3] Owing to their low lipid solubility, these water-soluble components are unable to penetrate extremely lipid-rich biological membranes, resulting in poor bioavailability.[4] Many methods for increasing bioavailability have been established, including the use of solubility and bioavailability enhancers, structural modification, and entrapment with a lipophilic carrier.[5] The chemical complexity of the crude or partly distilled extract seems to be critical for the active constituents' bioavailability.[6] Any constituents of water-soluble extracts can be killed in the gastric atmosphere when ingested orally.[7]

The 'phytosome,' a novel phyto-phospholipid complexation strategy that plays an important role in increasing absorption and enhancing bioavailability, has emerged as one of the most effective methods for improving the bioavailability of phyto-pharmaceuticals with low solubility and difficulty crossing biological membranes.[8] Several plant actives have struggled to show comparable *in vivo* reactions despite possessing potent *in vitro* pharmacological activities.[9] These plant actives have been rendered more successful systemically by combining them with dietary phospholipids, creating new amphipathic cellular structures.[10] Phytosome is a patent established by Indena, a leading provider of nutraceuticals ingredients, to introduce phospholipids to a standardized extract to boost absorption, bioavailability, and consumption.[11]

2. PHYTO-PHOSPHOLIPID COMPLEX VESICLES

Phytosomes are structures that resemble cells (**Figure 1**). Phytosome is a new solution to drug delivery mechanism that tackles the shortcomings of traditional drug delivery systems.[12] "Phyto" means herb, and "some" means cell-like. The bioactive phytoconstituents of herb extracts are enclosed by lipids in phytosomes.[13] Phytosomes are produced by mixing uniform plant extracts or water-soluble bioactive plant constituents with phospholipids to form lipid-compatible molecular complexes known as phytosomes, which enhance absorption and bioavailability.[14] The phytosome mechanism generates a cell, which is a valuable component of herbal extract that is safe from digestive secretion and gut bacteria destruction.[15] Phytosomes are more capable of

transitioning from a hydrophilic state to the lipid-friendly environment of the enterocyte cell membrane, and ultimately through the cell, which eventually reaches the blood.[16] To make lipid-soluble complexes, hydrophilic phytoconstituents can be complexed with clinically important phospholipids. These complexes may be used to make phytosomes, which are liposome-like vesicles.[17]

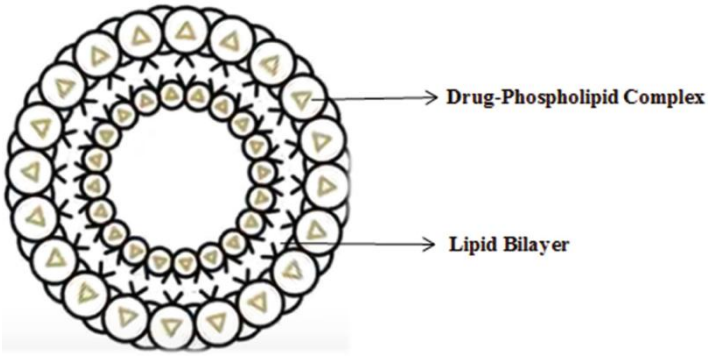


Figure 1: Structure of Phytosomes.

Chemical bonds are formed during the complexation of phospholipids and water-soluble active plant components in phytosomes, making them more stable.[18] The phytosomes raise the bioavailability of these polar active ingredients greatly. Soya phospholipids, egg lecithin, phosphatidylcholine, and other phospholipids have been identified for phytosome preparation (**Figure 2**).[19] Phytosomes are able to quickly traverse lipid biomembranes and have been shown to improve the bioavailability of extracts that are poorly lipid-soluble by increasing absorption in the gastrointestinal tract.[20]

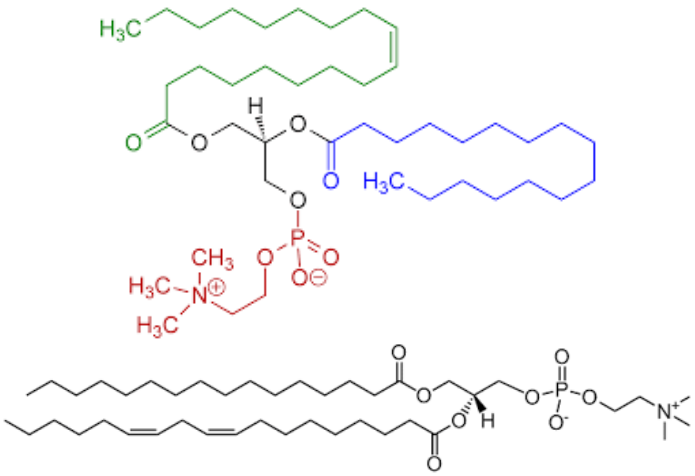


Figure 2: Structure of some common Phospholipid: Lecithin (Above) and Soya Phosphatidylcholine (Below).

3. ADVANTAGES OF PHYTOSOME VESICLES[21]

1. They quickly pass across the cell membrane and enter the cell.
2. There is a noticeable increase in the drug's bioavailability.
3. Phytosomes ensure that herbal medicines have a long time of operation.
4. Phytosomes improve the bioavailability of hydrophilic polar phytoconstituents by increasing their absorption by nasal, topical, and other routes.
5. Phytosomes create a tiny cell that preserves the valuable components of herbal extracts from digestion secretions and intestinal bacteria.
6. Phytosomes persuade proper medication distribution to the necessary tissues.
7. Assigning the herbal medicine as phytosomes does not have to jeopardize the nutritional purity of the herbal extracts.
8. Due to the maximum absorption of the main constituents, the dose requirement has been reduced.
9. They enhance biologically active constituent absorption and reduce dosage specifications.
10. Chemical bonds formed between the phosphatidylcholine molecule and phytoconstituents indicate that phytosomes have a strong stability profile.
11. Phytosomes enhance phytoconstituent transdermal absorption and are commonly used in cosmetics due to their increased skin penetration and high lipid profile.

12. Phytoconstituents in phytosomes can quickly pass through tissue walls in the intestine and are best absorbed.
13. The phytosome complex is biodegradable, and drug entrapment is not a concern.
14. Phytosomes enhance the effect of herbal substances by optimizing absorption, increasing biological activity, and supplying to the target tissue; as a result, they are appropriate for use as a drug delivery mechanism.
15. Since the compound is conjugated with lipids in the development of vesicles, entrapment efficiency is high.
16. Drug entrapment is not an issue when creating phytosomes.
17. Phosphatidylcholine, which is used to make phytosomes, not only acts as a messenger, but it also nourishes the skin since it is a component of the cell membrane.
18. In skincare items, phytosomes outperform liposomes.
19. Phytosomes have been shown to have a major therapeutic advantage.
20. Phosphatidylcholine, which is used in the preparation of phytosomes and serves as a transporter as well as a hepatoprotective, has a synergistic impact when combined with hepatoprotective compounds.
21. Their poor aqueous solubility allows for the formulation of a robust semisolid dosage type.
22. Facilitates liver targeting by rising bile salt solubility.

4. PROPERTIES OF PHYTOSOMES

4.1. Physicochemical properties

Phytosomes are manufactured substances combined with phospholipids. In a suitable solvent, stoichiometric quantities of phospholipids and the substrate are combined to form this complex. The major phospholipid-substrate association is due to the forming of hydrogen bonds between the polar head of phospholipids (*i.e.* phosphate and ammonium groups) and the polar functionalities of the substrate, according to spectroscopic results. Phytosomes take on a micellar shape when exposed to water, creating a liposomal structure. This can be deduced from a calculation of the complex's NMR to that of the pure precursors. The fatty chain's signs are almost unchanged. According to these findings, the two long aliphatic chains coil around the active material, forming a lipophilic envelope that protects the phospholipid's polar head and active constituents.[22]

4.2. Biological properties

Phytosomes are advanced herbal compounds that are more readily consumed, utilized, and therefore yield greater outcomes than typical herbal extracts. Pharmacokinetic experiments and pharmacodynamic research in laboratory animals and human subjects have shown that the phytosome has a greater bioavailability than non-complexed botanical derivatives.[23]

5. PROSPECTS OF PHYTOSOME TECHNOLOGY[24]

When compared with conventional herbal formulation, phytosomes have the following prospects:

1. They increase the oral and topical absorption of lipid insoluble polar botanical extracts, resulting in higher bioavailability and therefore a greater medicinal value.
2. When the active constituent(s)' absorption increases, a minimal dosage will achieve the desired effects.
3. Due to the forming of chemical bonds between the phosphatidylcholine molecule and the botanical extract, phytosomes have a higher stability profile.
4. Phytosomes are more capable of transitioning from a hydrophilic state to the lipid-friendly environment of the enterocyte cell membrane and then into the cell, allowing for systemic targeting.
5. Phytosomes are frequently used in cosmetics since they penetrate the skin well and have a strong lipid profile.
6. Phytosomes promote liver targeting by increasing the solubility of bile in herbal constituents.

6. METHODS OF PREPARATION

6.1. Anti-solvent precipitation technique

In a 100 mL circular bottom flask, the specific volume of plant extract and phospholipid were mixed with 20 mL dichloromethane and refluxed for 2 hours at a temperature of not more than 60°C. 5-10 mL of the mixture is condensed. The precipitate was filtered, gathered, and placed in desiccators overnight after hexane (20 mL) was carefully applied with continuous stirring. The crushed dry precipitate is sieved into #100 meshes in a mortar. The powdered complex was kept at room temperature in an amber-colored glass container.[25]

6.2. Rotary evaporation technique

In a rotary circular bottom flask, the specific volume of plant material and phospholipid were dissolved in 30 mL of tetrahydrofuran, then stirred for 3 hours at a temperature not exceeding 40oC. A thin film of the sample was collected, to which n-hexane was applied and a magnetic stirrer was used to constantly stir the mixture. The precipitate was extracted and deposited at room temperature in an amber-colored glass bottle.[26]

6.3. Solvent evaporation technique

In a 100 mL circular bottom flask, the specific volume of plant content and phospholipids is mixed with 20 mL acetone and refluxed for 2 hours at 50-60°C. The precipitate was purified and extracted after the mixture was condensed to 5-10 mL. The dry precipitate phytosome complex was kept at room temperature in an amber-colored glass container.[27]

6.4. Ether-injection technique

The drug lipid complex is dissolved in an organic solvent in this process. This mixture is then steadily pumped into

a heated aqueous agent, which causes vesicles to develop. Amphiphiles' state is determined by their focus. Amphiphiles implement a monomer state while the concentration is low, however, when the concentration rises, a number of structures, such as circular, cylindrical, disc, cubic, or hexagonal structures, may be created.[28]

7. CHARACTERIZATION TECHNIQUES[29]

7.1. Visualization

Transmission electron microscopy (TEM) may be used to image phytosomes. TEM may reveal information regarding internal structure as well as many other features of phytosomes, such as anatomy, crystallization, heat, and also magnetic domains. Scanning electron microscopy (SEM) examines the surface of phytosomes and reveals morphological information.

7.2. Particle size and zeta potential

Dynamic light scattering (DLS) with a computerized inspection method and photon similarity spectroscopy can be used to assess particle size and zeta potential.

7.3. Entrapment efficiency

The ultracentrifugation technique may be used to determine the drug's entrapment effectiveness, or its potential to be entrapped in phytosomes. It provides an estimate of the percentage of the medication safely entrapped in phytosomes.

7.4. Transition temperature

Differential scanning calorimetry (DSC) may be used to assess the transfer temperature in vesicular lipid systems.

7.5. Surface tension activity measurement

The ring procedure in a Du Nouy ring tensiometer can be used to calculate the drug's surface tension response in an aqueous solution.

7.6. Vesicle stability

The scale and shape of vesicles can be measured over time to assess their stability. DLS determines the average scale, while TEM monitors structural shifts.

7.7. Drug content

An updated high-performance liquid chromatographic process or an appropriate spectroscopic method may be used to evaluate the volume of drug current.

7.8. Proton-Nuclear Magnetic Resonance (^{1}H-NMR)

Spectroscopic studies are commonly used to validate the development of complexes between phytoconstituents and the phospholipids moiety, as well as to analyze the resultant association. This approach can be used to approximate the complicated formation between active phytoconstituents and the phosphatidylcholine molecule.

7.9. Carbon-Nuclear Magnetic Resonance (^{13}C-NMR)

The carbons of the phytoconstituents were not evident in the ^{13}C-NMR of the phytoconstituents and the stoichiometric complex with phosphatidylcholine when registered. The signals referring to the glycerol and choline portions have been broadened and others have been moved, but the majority of the fatty acid chains' resonance has retained its initial sharp line structure.

7.10. Fourier-Transformed Infra-Red (FT-IR) Spectroscopy

FT-IR spectroscopy may be used to validate the complex's formation by matching the complex's spectrum to the spectrum of the individual components and their mechanical mixtures. When phytosomes are micro-dispersed in water or inserted into very basic cosmetic gels, FT-IR spectroscopy is a valuable method for controlling their stability. In practice, the stability of the complex can be checked by contrasting the spectrum of the complex in solid form (phytosomes) with the spectrum of its micro-dispersion in water, following the lyophilization at various periods.

7.11. *In-vitro* and *in-vivo* evaluations

The predicted therapeutic action of the biologically active phytoconstituents found in the plants. Phytosomes are used to pick *in-vitro* and *in-vivo* evaluation models.

8. PHYTOSOME FORMULATIONS DEVELOPMENT

Phytosome complexes may be converted and formulated into a variety of oral and topically applied dosage formulations. Various goods may be created to get the best results from this technical advancement, both in terms of formulating manageability and increased bioavailability.

8.1 Soft gelatin capsules

Soft gelatin capsules are an outstanding alternative for preparing phytosome complexes. The phytosome complex may be suspended in oily automobiles and then filled into soft gelatin capsules. This may be done with vegetable or semi-synthetic oils. To produce the right capsules, Indena recommends using a granulometry of 100 percent. According to Indena's knowledge, not all phytosome complexes act the same when spread in oily vehicles and when the oily suspension is filled in soft gelatin capsules; as a result, preliminary feasibility trials should be conducted to determine the best vehicle.[30]

8.2 Hard gelatin capsules

Hard gelatin capsules may also be made from the phytosome complex. Even if the phytosome complex's obvious low density tends to restrict the overall amount of powder that can be filled into a capsule, a direct volumetric filling procedure (without pre-compression) can be used (usually not more than 300 mg for a size 0 capsule). It is possible to increase the amount of powder that can be filled in a capsule using a piston tamp capsule filling procedure, but pre-compression can impact the disintegration period. During product/process growth, Indena suggests keeping a close eye on the relevant parameters. The best manufacturing method is described by a preliminary dry granulation process.[31]

8.3 Tablets

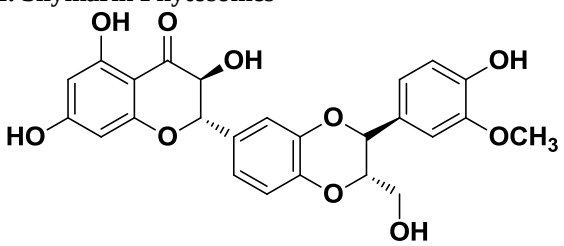
Dry granulation is the safest technique for generating tablets with higher unitary doses and sufficient technical and biopharmaceutical properties. A direct compression method should only be used for low unitary doses due to the phytosome complex's restricted flow capacity, possible stickiness, and low evident density; notice that if a direct compression process is used, the phytosome complex should be diluted with 60-70 percent excipients to maximize its technical properties and obtain tablets with sufficient morphology. Wet granulation, on the other hand, should be prevented due to the detrimental effects of water and heat (granulation/drying) on the phospholipid complex's stability.[32]

8.4 Topical dosage forms

The phytosome complex may also be applied topically. The only way to integrate the phytosome complex into an emulsion is to spread the phospholipidic complex in a limited volume of the lipidic phase and apply it to an emulsion that has already been formed at low temperatures (less than 40°C). The phytosome complexes dissolve in the most common lipidic solvents used in topical formulations. In the case of formulations with low lipid content, the phytosome complex should be distributed in the watery process and then applied to the final formulation at a temperature below 40°C.[33]

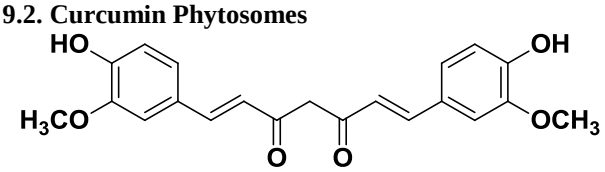
9. REPORTED PHYTOSOMES PRODUCTS

9.1. Silymarin Phytosomes



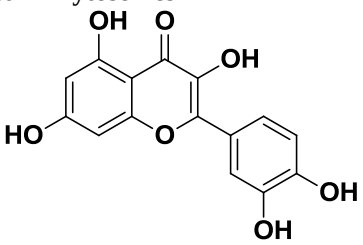
The bulk of phytosomal research has concentrated on *Silybum marianum* (milk thistles), which produces potent liver-protective flavonoids. Researchers analyzed the pharmacokinetics of silymarin phytosome in rats. The bioavailability of silybin in rats was greatly improved after oral administration of silybin-phospholipid compound, owing to an impressive improvement in the lipophilic properties of the complex and an improvement in the biological activity of silybin. It was found that silymarin phytosomes have greater anti-hepatotoxic activity than silymarin alone and may shield broiler chicks from the toxic effects of aflatoxin B1.[34]

9.2. Curcumin Phytosomes



Investigators produced curcumin (flavonoid from *Curcuma longa*, turmeric) and naringenin (flavonoid from grapefruit, *Vitis vinifera*) phytosomes. In all dosage ranges measured, the complex's antioxidant function was considerably higher than pure curcumin. In another research, the formed phytosome of naringenin produced higher antioxidant activity and a longer time of action than the free compound, perhaps attributable to a decline in the molecule's rapid removal from the body.[35]

9.3. Quercetin Phytosomes



Researchers used an easy and repeatable approach to construct the quercetin-phospholipid Phytosomal compound, and they also demonstrated that the mixture had greater therapeutic efficacy than the molecule in rat liver damage triggered by carbon tetrachloride.[36]

9.4. Grape seed extract Phytosomes

It is made up of oligomeric polyphenols (grape proanthocyanidins or Procyanidin from *Vitis vinifera* grape seed extract) of different molecular sizes that are complexed with phospholipids. The main properties of grape seed Procyanidin flavonoids include an increase in total antioxidant capacity and stimulation of physiological defenses in plasma, protection against ischemia/reperfusion-induced heart damage, and protective effects against atherosclerosis, both of which provide significant protection for the cardiovascular system and other organs through a network of mechanisms.[37]

9.5. *Gingko biloba* leaves Phytosomes

Studies have shown that gingko phytosomes (made from a standardized extract of *Ginkgo biloba* leaves) outperformed typically standardized extracts from plants (24 percent ginkgo flavones glycoside and 6 percent terpenes lactones). The amount of *G. biloba* constituents (flavonoids and terpenes) from the phytosomal form peaked after 3 hours and lasted for at least 5 hours after oral administration in a bioavailability trial with safe human volunteers. The phytosomal *G. biloba* developed a 2-4 times higher plasma concentration of terpenes than the non-phytosomal *G. biloba*, according to the findings. It is used to manage cerebral insufficiency and peripheral vascular diseases, as well as impaired cerebral circulation. Because of its enhanced oral bioavailability and tolerability, it is the best gingko product for long-term use. Studies have also shown that ginkgo phytosomes are more effective than standardized extract in shielding isolated rat hearts from ischemia.[38]

9.6. Green tea Phytosomes

Green tea leaves (*Thea sinensis*) are distinguished by the existence of epigallocatechin 3-O-gallate, a polyphenolic compound. These compounds are efficient modulators of a variety of biochemical processes related to the collapse of homeostasis in diseases including cancer and atherosclerosis. Green tea has a variety of health benefits, including antioxidant, anticarcinogenic, antimutagenic,hypocholesterolemic, and cardioprotective properties.[39]

9.7. *Olea Europaea* oil Phytosomes

Oleaselect phytosome, a commercially produced phytosome focused on olive oil polyphenols, is available on the market. It has anti-oxidant, anti-inflammatory, and anti-hyperlipidemic properties. It protects the heart by inhibiting the oxidation of LDL cholesterol.[40]

10. RECENT MARKETED PRODUCTS

10.1. Ginkgoselect®

It's a generic extract of *G. biloba* leaves in a conveniently absorbable shape. The main signs are cerebral insufficiency and peripheral vascular diseases, and it is a valuable assist in cases where cerebral performance is compromised. Its improved oral bioavailability and tolerability render it an excellent option for long-term care. It's a generic extract of *G. biloba* leaves that's more easily absorbed. Cerebral insufficiency and peripheral vascular diseases are the most common indications, and they may also help with impaired cerebral circulation. Because of its enhanced oral bioavailability and tolerability, it is the perfect Ginkgo product for long-term usage.[41]

10.2. Greenselect®

It comprises a fully uniform polyphenolic fraction (no less than 66.5 percent) extracted from green tea leaves, which is predominantly identified by the inclusion of epigallocatechin and derivatives. These compounds have been shown to be efficient *in vitro* modulators of a number of biochemical processes implicated in the pathogenesis of significant chronic degenerative diseases including cancer and atherosclerosis. Green tea polyphenols' oral bioavailability is considerably increased as they are complexed with phospholipids. It is made up of a fully uniform polyphenolic fraction (no less than 66.5 percent) derived from green tea leaves, with epigallocatechin and its variants being the most prominent. These compounds are efficient modulators of a variety of biochemical processes related to the collapse of homeostasis in diseases including cancer and atherosclerosis. Green tea polyphenols' low oral bioavailability is significantly enhanced when they are complexed with phospholipids.[42]

10.3. Siliphos®

It protects the liver from a variety of causes. It is the most absorbable source of silybin currently available, enabling it to penetrate the target organ, the liver, in quantities that have been proven to be antihepatotoxic.[43]

10.4. Mirtoselect®

It contains bilberry extract, which produces anthocyanosides. These are potent antioxidants that increase capillary tone, decrease abnormal blood vessel permeability, and boost capillary tone. They have a lot of promise in terms of managing retinal blood flow disorders and venous insufficiency.[44]

10.5. Sabalselect®

It comprises a saw palmetto berry extract obtained by supercritical CO_2 (carbon dioxide) extraction. It includes fatty acids, alcohols, and sterols, both of which are helpful to prostate health. This extract can help non-cancerous prostate enlargement in particular.[45]

10.6. Lymphaselect™

It produces a *Melilotus officinalis* extract. This medication is used to treat venous diseases, such as persistent venous insufficiency in the lower limbs.[46]

10.7. Oleaselect™

It is a more modern preparation made from polyphenols present in olive oil. These are active free radical scavengers (antioxidants) that often have anti-inflammatory properties and prevent the dangerous oxidation of LDL cholesterol.[47]

10.8. Polinacea™

Echinacea angustifolia is used to make this immunomodulating preparation. It comprises echinacosides and a high-molecular-weight polysaccharide that is unique. This supplement improves immune function in the face of a toxic threat. The phytosome technology allows cost-effective distribution and synergistic effects from the phospholipid nutraceuticals found in nature for any of these groundbreaking phytomedicines.[48]

11. CONCLUSION

Phytosomes are new structures made up of lipophilic complexes of plant components such as *S. marianum*, *G. biloba*, and ginseng, as well as normal phospholipids. Non-conventional methods are commonly used to prepare phytosomes. When phytosomes are used as a drug, the absorption of the phytosome in the gastrointestinal tract is slightly higher than the actual portion, resulting in a higher plasma level. Many aspects of phytosomes will be revealed in the future with the hope of being used in pharmaceuticals. Phytosomes serve as a connection between traditional and alternative distribution systems. Phytosomes enable pharmaceutical companies to create new products based on water-soluble drugs, as well as include new innovations in the pharmaceutical industry. The technology is capable of distributing the substance both topically and orally. Originally used in cosmetics, phytosome complexes are also widely used as a medication delivery mechanism in treatments such as antioxidants, gastrointestinal, anti-inflammatory, hepatoprotective, and anti-cancer. The phyto-phospholipid complexing technique has become a

game-changer for herbal medicines that haven't been able to have a significant impact *in vivo* despite positive *in vitro* results. Phytosomes are a promising drug delivery mechanism for enhancing the effectiveness, quality, and targetability of active plant constituents and herbal extracts.

ABBREVIATIONS

DLS: Dynamic Light Scattering
TEM: Transmission Electron Microscopy
SEM: Scanning Electron Microscopy
DSC: Differential Scanning Calorimetry
^{1}H-NMR: Proton-Nuclear Magnetic Resonance
^{13}C-NMR: Carbon-Nuclear Magnetic Resonance
FT-IR: Fourier-Transformed Infra-Red

CONFLICTS OF INTEREST

No conflict of interest is declared.

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