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# PHYTOSOME- A NOVEL APPROACH FOR HERBAL DRUG DELIVERY

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## ABSTRACT

The bioavailability of some orally administered botanical extracts is erratic and poor due to limited gastro-intestinal absorption. Bioavailability can be improved by using new delivery systems which can enhance the rate and the extent of solubilization into aqueous intestinal fluids and the capacity to cross biomembranes. Phospholipids based drug delivery system have been found promising for better and effective delivery of drug and providing much appropriate systematic drug delivery. The phospholipids molecular structure includes a water-soluble head and two fat-soluble tails, because of this dual solubility, the phospholipids acts as an effective emulsifier, which is also one of the chief components of the membranes in our cells. In other words, complexing the polyphenolic phytoconstituents in molar ratio with phosphatidylcholine results into a new herbal drug delivery system- "Phytosome". Phytosomes are an advanced botanicals technology that offers improved absorption, enhanced delivery and increased bioavailability of herbal extracts. Phytosomes exhibit better pharmacokinetic and pharmacodynamic profile than conventional herbal extracts Phytosome technology has been effectively used to enhanced the bioavailability of many popular herbal extracts including milk thistle, Ginkgo bilobann, grape seed, green tea, hawthorn, ginseng etc and can be developed for various therapeutic uses or dietary supplements This article reviews the current trends in phytosomes drug delivery.

**INTRODUCTION:** Over the past century pharmacological and chemical studies have been performed on a lot of plant extracts in order to know their chemical composition and confirm their indications of traditional medicine. Herbal drugs containing bioactive constituents are mainly water soluble molecules. However, many flavonoid which are water soluble phytoconstituents like to be poorly absorbed [1] due to their poor miscibility with oils and other lipids or due to their multiple-ring large size molecules which cannot be absorbed by simple diffusion, severely limiting factors are available for their ability to pass across the lipid-rich outer membranes of the enterocytes of the small intestine. Polyphenols (Water-soluble phytoconstituents) molecules can be converted into lipid-compatible molecular complexes, which are called Phytosomes.

Phytosomes are more bioavailable in comparison to simple herbal extracts. They have enhanced capacity to cross the lipid rich biomembranes and finally reaching the blood [2]. The lipid-phase substances employed to make phytoconstituents, lipid compatible are phospholipids from soy, mainly phosphatidylcholine (PC). Phospholipids are complex molecules that are used in all known life forms to make cell membranes. The term "Phyto" means plant while "some" means cell-like. The Phytosomes process itself produces a little cell whereby the valuable component of the herbal extract is protected from destruction by digestive secretions and gut bacteria [3].

Flavonoids are the most important group of phytochemicals. Flavonoids are the class of compounds that have referred to be a natural biological response modifier which acts as powerful antioxidants that providing remarkable protection against oxidative and free radical damage. Various flavonoids which have shown antioxidant activity 50 to 200 times more potent than vitamin C or E. we can use certain flavonoids-rich extracts that referred as "tissue specific antioxidants" due to their ability of concentrated in specific body tissue [4].

Phytosomes is a patented technology developed by a leading manufacturer of drugs and nutraceuticals, whereby the individual component of a standardized plant extracts are bound to phosphatidylcholine - an emulsifying component to produce lipid compatible molecular complexes, called as Phytosomes and so vastly improve their absorption and bioavailability [5].

There are many plant drugs that are incorporated to Phytosomes process as herbal extracts including *Ginkgo biloba, grape seed, hawthorn, milk thistle, green tea,* and *ginseng* .Phytosomes are more bioavailable as compared to conventional herbal extracts owing to their enhanced capacity to cross the lipoidal biomembrane and finally reaching the systemic circulation. So, Phytosomes has been a novel approach for the herbal drug delivery [6].

**Method of preparation:** Phytosomes are complexes chemical mixtures which are prepared by reacting from with one or two mole of natural or synthetic phospholipids phosphatidyl ethanolamine or phosphatidyiserine with one mole of component. For example, flavolignanans, either alone or in the natural mixture in aprotic solvent such as- dioxane or acetone from which complex can be isolated by precipitation with non solvent such as aliphatic hydrocarbons or lyophilization or by spray drying. In the complex formation of Phytosomes the ratio between these two moieties is in the range from 0.5-2.0 moles.

The most preferable ratio of phospholipids to flavonoids is 1:1 [7]. In the Phytosomes preparations, phospholipids are selected from the various group such as, phosphatidyl, ethanolamine, phosphatidylcholine, soy lecithin, from bovine or

swine brain or dermis, phosphatidyiserine in which acyl group may be same or different and mostly derived from palmitic, stearic, oleic and linoleic acid. Flavonoids are selected from the group consisting of quercetin, kaempferol, quercretin-3, rhamnoglucoside, quercetin- 3- rhamnoside, hyperoside, vitexine, diosmine, 3- rhamnoside, (+).

Some liposomal drugs complex operate in the presence of the water or buffer solution where as phytosomes operate with the solvent having a reduced dielectric constant. Flavonoid which is the Starting material of component is insoluble in chloroform, ethyl ether or benzene. They become extremely soluble in these solvents after forming phytosomes. This chemical and physical property change is due to the formation of a true stable complex [8].

**How Phytosomes differ from liposome:** Likewise Phytosomes, a liposome is formed by mixing phosphatidylcholine with water soluble substance in definite ratio. The phosphatidylcholine molecules surround the water soluble substance in which no chemical bond is formed. There are hundreds or even thousands of phosphatidylcholine molecules surrounding the water-soluble compound.

In contrast, with the Phytosomes process the plant components and the phosphatidylcholine actually form a 1:1 or a 2:1 molecular complex depending on the substance(s) complexed, in which chemical bond is formed. This difference shows that Phytosomes being much better absorbed than liposome showing better bioavailability. Phytosomes have also been found superior than liposome in topical and skin care products [9].

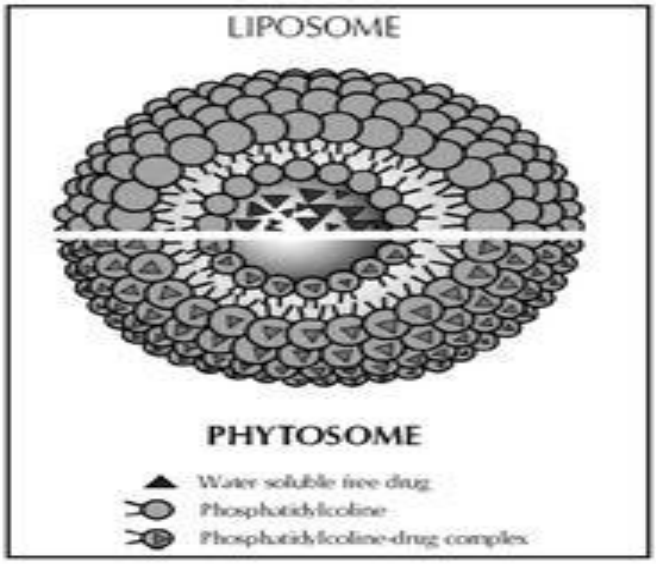


**FIG. 1: PHYTOSOMES DIFFER FROM LIPOSOMES**

**TABLE 1: COMMERCIAL PHYTOSOME PREPARATIONS [10, 11]**

| Phytosomes | Phytoconstituent complexed with Phosphatidylcholine | Indication |
|---|---|---|
| Silybin Phytosome TM | Silybin from Silymarin | Food Product, antioxidant for Liver and skin. |
| Ginkgo Phytosome TM | 24 % ginkgoflavonglycosides from *Ginkgo biloba* | Protects brain and vascular lining, Anti-skin ageing agent. |
| Panax ginseng Phytosome TM | 37.5 % ginsenosides from roots of *Panax ginseng* | Food Product. |
| Green Tea Phytosome TM | Epigallocatechin 3-O- gallate from *Camelia sinensi* | Food Product, Systemic antioxidant, Cancer protectant. |
| Super Milk thistle Extract | Silybin from Silymarin | Food Product; antioxidant for liver and skin. |
| Grape seed (PCO) Phytosomes | Procyanidolic oligomers (PCOs) from grape Seeds | Food Product; protects against heart |
| Hawthorn Phytosomes | Flavonoids | Food Product. |
| Centella Phytosome | Terpenes | Vein & skin disorders. |

**Properties of Phytosomes**

- **Chemical properties:** Phytosomes are novel complexes formed between the natural product and natural phospholipids, like soy phospholipids. Such a complex is obtained by reaction of stoichometric amounts of phospholipid and the substrate in an appropriate solvent. On the basis of spectroscopic data it has been shown that the interaction of phospholipid-substrate is due to the formation of hydrogen bonds between the polar head of phospholipids (i.e. phosphate and ammonium groups) and the polar functionalities of the substrate.

When it treated with water, phytosomes assumes a micellar shape which formed the liposomal-like structures, In liposome the active principle is floating in the layer membrane, while in phytosomes the active principle is anchored to the polar head of phospholipids, becoming an integral part of the membrane for example in the case of the catechindistearoyl phosphatidylcholine complex, there is the formation of H-bonds between the phosphate ion on the phosphatidylcholine side and the phenolic hydroxyls of the flavone moiety.

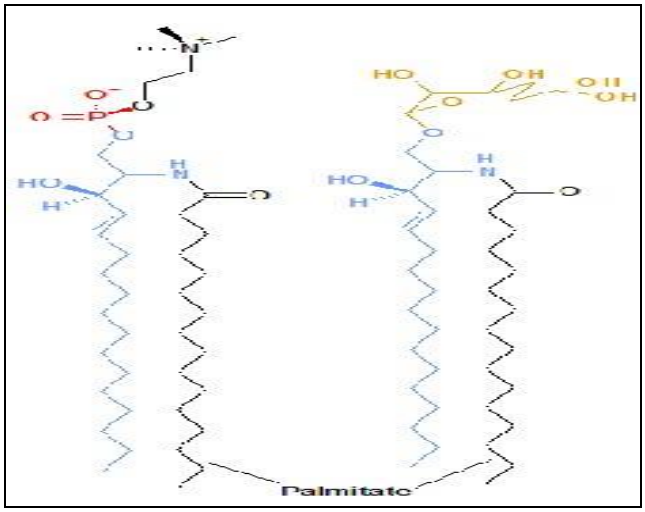


**FIG. 2: PHOSPHATIDYLCHOLINE COMPLEX**

**Phosphatidylcholine:** This can be assumed from the comparison of the NMR of the complex with the precursors of complex. The signals of the fatty chain are almost unchanged. Such evidences inferred that the two long aliphatic chains are wrapped around the active principle, producing a lipophilic envelope, which shields the polar head of the phospholipid and the catechin [12].

- **Biological Properties**: Phytosomes are advanced botanical technology that offers improved absorption, enhanced delivery and increased bioavailability of herbal extracts phytosomes over the non complexed botanical derivatives has been demonstrated by pharmacokinetics studies or by pharmacodynamic tests in experimental animals and in human subjects [13].

**The Phytosome Technology:** The flavonoid and terpenoid constituents of plant extracts provide them for the direct binding to phosphatidylcholine. Phytosomes results from the reaction of a stoichometric amount of the phospholipid (phosphatidylcholine) with the standardized extract or polyphenolic constituents in a non polar solvent [14]. Phosphatidylcholine is a bifunctional compound, the phosphatidyl moiety being lipophilic and the choline moiety being hydrophilic in nature. In particular, the choline head of the phosphatidylcholine molecule binds to these compounds while the lipid soluble phosphatidyl portion comprising the body and tail which then envelopes the choline bound material.

Hence, the Phytoconstituents produce a lipid compatible molecular complex with phospholipids, also called as phytophospholipid complex. By specific spectroscopic techniques, it can be demonstrated that the molecules are anchored through chemical bonds to the polar choline head of the phospholipids, as [15, 16]. Precise chemical analysis designate that the unit phytosome is usually a flavonoid molecule linked

with at least one phosphatidylcholine molecule. The result is a little micro sphere or cell is produced. The term "Phyto" means plant while "some" means cell-like. The phytosome technology produces a little cell, whereby the plant extract or its active constituent is protected from destruction by gastric secretions and gut bacteria owing to the gastro protective property of phosphatidylcholine [17].

**Characterization of Phytosomes:** There are many factors which govern the behavior of phytosomes in both physical and biological system, such as physical size membrane permeability; percent entrapped solutes, chemical composition as well as the quantity and purity of the starting materials. Therefore, the phytosomes are characterized for physical attributes i.e. shape, size, its distribution, percentage drug capture entrapped volume, percentage drug released and chemical composition [18].

**Enhanced bioavailability:** Many researches done which shows improved absorption and bioavailability with phytosomes in comparison to the conventional means. Recent researches shows that Most of the phytosomal studies are focused to *Silybum marianum* (milk thistle) which contains premier liver-protectant flavonoids The fruit of the milk thistle plant contains flavonoids known for hepatoprotective effects [19, 20]. Silybin is the chief and most potent constituent of silymarin, the flavonoid complex from milk thistle. A standardized extract from *Silybum marianum* (milk thistle) is an excellent liver protectant but very poorly absorbed orally.

Yanyu *et al*., prepared the silymarin phytosome and show its pharmacokinetics in rats. In the study after oral administration of prepared Silybin phospholipid complex, the bioavailability of Silybin in rats was increased remarkably due to an impressive improvement of the lipophilic property of Silybin-phospholipid complex and the biological effect of Silybin was improved [21].

Tedesco *et al*., reported Silymarin phytosome show better anti-hepatotoxic activity than silymarin alone. Silymarin phytosome provide protection against the toxic effects of aflatoxin B1 on performance of broiler chicks [22]. Busby *et al*., reported that the Silymarin phytosome showed a better fetoprotectant activity from ethanol-induced behavioral deficits than uncomplexed silymarin [23]. Grange *et al*., conducted a series of studies on silymarin phytosome that containing a standardized extract from the seeds of *S. marianum*, administered orally and found that it could protect the fetus from maternally ingested ethanol [24].

Bombardelli *et al*., reported Silymarin phytosomes, in which silymarin (a standardized mixture of flavanolignans extracted) was complexed with phospholipids. Phytosomes showed longer lasting action and much higher specific activity in comparison to single constituents, with respect to percent reduction of odema, inhibition of myeloperoxidase activity, antioxidant and free radical scavenging properties [25].

Barzaghi *et al*., considered assessing the absorption of Silybin when directly bound to phosphatidylcholine. After administration of single oral doses of Silybin phytosome, Plasma Silybin levels were determined. The results shows that the absorption of Silybin from Silybin phytosome is approximately seven times greater compared to the absorption of Silybin from regular milk thistle extract (70-80 % silymarin content) [26].

Moscarella *et al*., perform a human study of 232 patients with chronic hepatitis (viral, alcohol or drug induced). They are treated with Silybin phytosome at a dose of 120 mg either twice daily or thrice daily function returned to normal faster in

patients taking Silybin phytosome compared to a group of commercially available silymarin, 117 controls (49 treated with for up to 120 days, liver untreated or given placebo) [27].

Studies have shown ginkgo phytosome (prepared from the standardized extract of *Ginkgo biloba* leaves) produced better results than the conventional standardized extract from the plant. In a bioavailability study conducted with healthy human volunteers it was found that the levels of GBE constituents (flavonoids and terpenes) peaked after 3 hours and persisted longer last for 5 hours after oral administration. It was also found that the phytosomal GBE produced greater plasma concentration of terpenes than the non-phytosomal GBE.

Its improved oral bioavailability and good tolerability makes it the ideal Ginkgo product even for long term treatment. Its major indications are cerebral insufficiency and peripheral vascular disorders, and it also can ameliorate reduced cerebral circulation. In studies with ginkgo phytosome in human patients with peripheral vascular disease (e.g. Reynaud's disease and intermittent circulation) it was shown to produce a 30-60% greater improvement compared to regular standardized GBE [28, 29].

Grape seed phytosome is prepared from grape seed extract containing oligomeric polyphenols (grape proanthocyanidins or procyanidinsrom) of varying molecular size, complexed with phospholipids. The main properties of procyanidin flavonoids of grape seed that they increase the total antioxidant capacity and stimulation of physiological antioxidant defenses of plasma, protective effects against atherosclerosis thereby offering marked protection for the cardiovascular system, protection against ischemia/reperfusion induced damages in the heart, and other organs through a network of mechanisms that extend beyond their great antioxidant potency [30]. In a study, they uses rabbit model for study. They were fed a high cholesterol diet to rabbit for 6 weeks, to markedly raise their blood cholesterol and induce atherosclerotic lesions in their aortas and carotid arteries. One group of rabbits received grape seed phytosome in their feed for the first 6 weeks, then 4 weeks of the high-cholesterol diet.

These developed significantly less aortic plaque than did the control groups which received conventional standardized grape seed extract in similar regimen. In a randomized human trial, young healthy volunteers received grape seed phytosome once daily for 5 days. The blood TRAP (Total Radical-trapping Antioxidant Parameter) was measured at several time intervals during 1st day, then also on 5th day. Already by 30 mins after administration on 1st day, blood TRAP levels were significantly elevated over the control which received conventional standardized grape seed extract [31].

Green tea extract generally contains a totally standardized polyphenolic fraction containing epigallocatechin obtained from green tea leaves (*Thea sinensis*) and mainly characterized by the presence of epigallocatechin 3-O-gallate, the key compound. These compounds are potent modulators of several biochemical processes linked to the breakdown of homeostasis in major chronic-degenerative diseases such as cancer and atherosclerosis.

Despite such potential actions green tea polyphenols have very poor oral bioavailability from conventional extracts. The complexation of green tea polyphenols with phospholipids strongly improves their poor oral bioavailability. A study on absorption of phytosomal preparations was performed in healthy human volunteers along with complexed green tea extract following oral administration. Over the study period of 6 hours the plasma concentration of total non flavonoids

was more than doubled when coming from the phytosomal versus the nonphytosomal extract. Antioxidant capacity was measured as TRAP (Total Radical-trapping Antioxidant Parameter). The peak antioxidant effect was a 20% enhancement and it showed that the phytosome formulation had about double the total antioxidant effect [32].

Maiti *et al*., developed the quercetin phospholipid phytosomal complex which showed that the formulation exerted better therapeutic efficacy than the molecule in rat liver injury induced by carbon tetrachloride [33]. Recently they developed the phytosomes of curcumin (flavonoid from turmeric, *Curcuma longa*) and naringenin (flavonoid from grape fruit, *Vitis vinifera*) in two different studies [34, 35]. The antioxidant activity of the quercetin phospholipid phytosomal complex was significantly higher than pure curcumin in all dose levels tested.

**Advantages of Phytosomes** [36-38]: Phytosomes have the following advantages;

- Phosphatidylcholine used in preparation of phytosomes, besides acting as a carrier also acts as a hepatoprotective, hence giving the synergistic effect when hepatoprotective substances are employed.
- They enhance the absorption of lipid insoluble polar phytoconstituents through oral as well as topical route showing better bioavailability, hence significantly greater therapeutic benefit.
- As the absorption of active constituent(s) is improved, its dose requirement is also reduced.
- Chemical bonds are formed between phosphatidylcholine molecule and phyto constituents, so the phytosomes show better stability profile.
- Added nutritional benefit of phospholipids

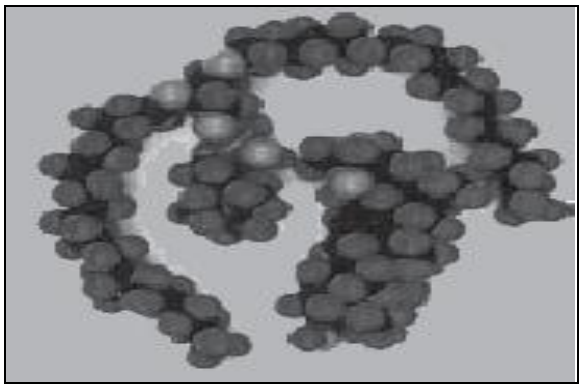

**FIG. 3: ORGANIZATION OF THE PHYTOSOME MOLECULAR COMPLEX**

**Recent trends in research on Phytosomes:** Charles K Armes founded Phyto technologies, Inc., dba. Advanced aromatherapy and herbal medicines co. which is manufacturer of concentrated liquid Phytoceutical extractions from plant plus natural medicine and body care products incorporating Phytochemicals components in their formulation. The corporation has been equipped with the foremost technology for extracting the full spectrum of phytochemicals from plants and an operational pilot plant for the production of liquid concentrates thereof. The product of ten years of development, this technology has far ranging applications.

Also transferred into the corporation, is a line of therapeutic herbal mineral bath formulations for contemporary health concerns, an aromatherapy line, plus a natural hair coloring formulation technology (underdevelopment), and an innovative nasal spray.Phyto technologies, Inc. will be market direct to consumers and natural practitioners directly through the internet, where it can be adequately represent its sophisticated products by educational efforts. Additionally, selected products such as the hair coloring line and the nasal spray will be marketed through drug stores and other mass outlets. Moreover, health food stores and such other outlets will be able to purchase on line [39].

**Applications of Phytosomes:** There are many plant drugs that are incorporated to Phytosomes process as herbal extracts including *Ginkgo biloba, grape seed, hawthorn, milk thistle, green tea,* and *ginseng*. Most of the phytosomal studies are focused to Silybum marianum which shows that it contains premier liver-protectant flavonoids. The fruit of the milk thistle plant (S. marianum, Family steraceae) contains flavonoids known for hepatoprotective effects. It was found that Silymarin has been shown to have positive effects in treating liver diseases of various kinds, including inflammation of the bile duct, hepatitis, cirrhosis and fatty infiltration of the liver.

The antioxidant capacity of silymarin significantly boosts the liver's resistance to toxic insults [40]. Silymarin primarily contains three flavonoids of the flavonol subclass. Silybin predominates, followed by silydianin and silychristin. Silybin is a flavonolignan which is probably produced within the plant by the combination of a flavonol with a coniferyl alcohol. It is now known that Silybin is the most potent of the three [41].

Silybin protects the liver by conserving glutathione in the parenchymal cells [40], while PC helps repair and replace cell membranes [42]. These constituents offer the synergistic benefit of sparing liver cells from destruction. In its native form within the milk thistle fruit, Silybin occurs primarily complexed with sugars, as a flavonyl glycoside or flavonolignan Silybin has been extensively researched and found to have impressive bioactivity, albeit limited by poor bioavailability.

**CONCLUSION:** Phytomedicines, complex chemical mixtures prepared from plants, have been used in medicine since ancient times and continue to have widespread popular use Phytosomes are advanced forms of herbal products that are better absorbed, utilized, and as a result produce better results than conventional herbal extracts. Phytosome preparation is done by non-conventional method. Absorption of phytosome in gastro-intestinal tract is appreciably greater resulting in increased plasma level than the individual component. Complex formation ratio of component and phospholipids is 1:1 and 2:1. Phytosomes forms a bridge between the convectional delivery system and novel delivery system. The Phytosome process has been applied to many popular herbal extracts including Ginkgo biloba, grape seed, hawthorn, milk thistle, green tea, and ginseng.

The flavonoid and terpenoid components of these herbal extracts lend themselves quite well for the direct binding to phosphatidylcholine. Through study of literature reveals that phytosome show promise in reliving the pain and symptoms associated with asthma, arthritis, rheumatism, ulcers, phlebitis, edema, varicose veins, premenstrual syndrome, diabetic retinopathy and hemorrhoids. Phytosomes are used as a medicament and have wide scope in cosmetology. Many areas of phytosome are to be revealed in future in the prospect of pharmaceutical application.

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