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Phytosomes: The New Technology for Enhancement of Bioavailability of Botanicals and Nutraceuticals

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Abstract

Lipid solubility and molecular size are the major limiting factors for molecules to pass the biological membrane to be absorbed systematically following oral or topical administration. Several plant extracts and phytoconstituents, despite having excellent bio-activity *in vitro* demonstrate less or no *in vivo* actions due to their poor lipid solubility or improper molecular size or both, resulting poor absorption and poor bioavailability. It is often found that, when individual constituents are isolated from the plant extract there is loss of specific bio-activity. Sometimes some constituents of the multi-constituent plant extract are destroyed in gastric environment when taken orally. Phytosomes are advanced forms of herbal formulations that are better absorbed, and as a result produce better bioavailability and actions than the conventional herbal extracts. They are produced by a patented process whereby the standardized plant extract or its constituents are bound to phospholipids, mainly phosphatidylcholine, producing a lipid compatible molecular complex. This phyto-phospholipid complex (phytosome) resembles a little cell. 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 biloba*, grape seed, green tea, hawthorn, ginseng etc and can be developed for various therapeutic uses or dietary supplements.

Keywords: Phytosomes, plant extract, bioavailability

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Introduction

Over the past century, phytochemical and phytopharmacological sciences established the compositions, biological activities and health promoting benefits of numerous botanical products. Most of the biologically active constituents of plants are polar or water soluble molecules. However, water soluble phytoconstituents (like flavonoids, tannins, terpenoids etc) are poorly absorbed either due to their large molecular size which can not absorb by passive diffusion, or due to their poor lipid solubility; severely limiting their ability to pass across the lipid-rich biological membranes, resulting poor bioavailability¹. It has often been observed that the isolation and purification of the constituents of an extract may lead to a partial or total loss of specific bio-activity for the purified constituent - the natural constituent synergy becomes lost. Very often the chemical complexity of the crude or partially purified extract seems to be essential for the bioavailability of the active constituents. Extracts when taken orally some constituents may be destroyed in the gastric environment. As standardized extracts are established, poor bioavailability often limits their clinical utility due to above said reasons. It has been observed that complexation with certain other clinically useful nutrients substantially improves the bioavailability of such extracts and their individual constituents. The nutrients so helpful for enhancing the absorption are the phospholipids. Phytosome is a patented technology developed by a leading manufacturer of drugs and nutraceuticals, to incorporate standardized plant extracts or water soluble phytoconstituents into phospholipids to produce lipid compatible molecular complexes, called as phytosomes and so vastly improve their absorption and bioavailability².

Phospholipids are complex molecules that are used in all known life forms to make cell membranes. In humans and other higher animals the phospholipids are also employed as natural digestive aids and as carriers for

both fat-miscible and water miscible nutrients. They are miscible both in water and in lipid environments, and are well absorbed orally. The phospholipid mainly employed to make phytosomes, is phosphatidylcholine, derived from soybean (*Glycine max*)³. 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. Phytosome has been an emerging trend in delivery of herbal drugs and nutraceuticals.

Phytosome Technology

The flavonoid and terpenoid constituents of plant extracts lend themselves quite well for the direct binding to phosphatidylcholine. Phytosomes results from the reaction of a stoichiometric amount of the phospholipid (phosphatidylcholine) with the standardized extract or polyphenolic constituents (like simple flavonoids) in a non polar solvent². Phosphatidylcholine is a bifunctional compound, the phosphatidyl moiety being lipophilic and the choline moiety being hydrophilic in nature. Specifically 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 phyto-phospholipid complex. Molecules are anchored through chemical bonds to the polar choline head of the phospholipids, as can be demonstrated by specific spectroscopic techniques^{4,5}. Precise chemical analysis indicates 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 gastroprotective property of phosphatidylcholine⁶.



Figure 1: Organization of the phytosome molecular complex. A flavonoid molecule (lower right) is enveloped by a phospholipid molecule.

Likewise phytosomes, a liposome is formed by mixing a water soluble substance with phosphatidylcholine in definite ratio under specific conditions. Here, no chemical bond is formed; the phosphatidylcholine molecules surround the water soluble substance. There may be hundreds or even thousands of phosphatidylcholine molecules surrounding the water-soluble compound. In contrast, with the phytosome process the phosphatidylcholine and the plant components actually form a 1:1 or a 2:1 molecular complex depending on the substance(s) complexed, involving chemical bonds. This difference results in phytosome being much better absorbed than liposomes showing better bioavailability. Phytosomes have also been found superior to liposomes in topical and skin care products⁷.

Methods of preparation

Phytosomes are prepared by complexing polyphenolic phytoconstituents in 1:2 or 1:1 ratio with phosphatidylcholine. Marena and Lampertico, Jiang et al, Maiti et al. reported the methods of phytosome preparation⁸⁻¹¹. Yanyu et al prepared silybin-phospholipid complex using ethanol as a reaction

medium. Silybin and phospholipids were resolved into the medium, after the organic solvent was removed under vacuum condition, silybin-phospholipid complex was formed¹².

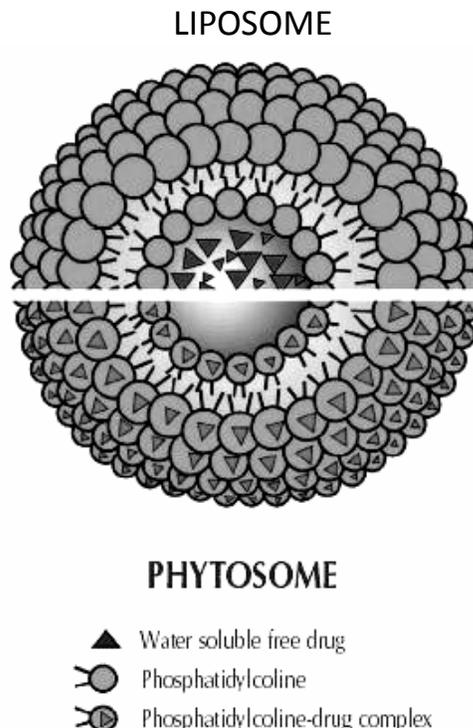


Figure 2: Major difference between liposome and phytosome. The molecular organization of the liposome (upper segment) versus many individual phytosomes (lower segment).

Advantages of phytosomes

Phytosomes have the following advantages¹³⁻¹⁵.

- It enhances 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.

- 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.
- Chemical bonds are formed between phosphatidylcholine molecule and phytoconstituent, so the phytosomes show better stability profile.
- Added nutritional benefit of phospholipids.

Enhanced bioavailability

Recent research shows improved absorption and bioavailability with phytosomes as compared to the conventional means. 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^{16,17}. 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 studied its pharmacokinetics in rats. In the study the bioavailability of silybin in rats was increased remarkably after oral administration of prepared silybin-phospholipid complex due to an impressive improvement of the lipophilic property of silybin-phospholipid complex and improvement of the biological effect of silybin¹².

Tedesco et al. reported silymarin phytosome show better anti-hepatotoxic activity than silymarin alone and can provide protection against the toxic effects of aflatoxin B1 on performance of broiler chicks¹⁸. Busby et al reported that the use of a silymarin phytosome showed a better fetoprotectant activity from ethanol-induced behavioral deficits than uncomplexed silymarin¹⁹.

Grange et al. conducted a series of studies on silymarin phytosome, containing a standardized extract from the seeds of *S. marianum*, administered orally and found that it could protect the fetus from maternally ingested ethanol²⁰.

Bombardelli et al. reported Silymarin phytosomes, in which silymarin (a standardized mixture of flavanolignans extracted from the fruits of *S. marianum*) was complexed with phospholipids. Phytosomes showed much higher specific activity and a longer lasting action than the single constituents, with respect to percent reduction of odema, inhibition of myeloperoxidase activity, antioxidant and free radical scavenging properties¹⁵.

Barzaghi et al. conducted a human study designed to assess the absorption of silybin when directly bound to phosphatidylcholine. Plasma silybin levels were determined after administration of single oral doses of silybin phytosome and a similar amount of silybin from milk thistle in healthy volunteers. The results indicated 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)²¹.

Moscarella et al. investigated in one study of 232 patients with chronic hepatitis (viral, alcohol or drug induced) treated with silybin phytosome at a dose of 120 mg either twice daily or thrice daily for up to 120 days, liver function returned to normal faster in patients taking silybin phytosome compared to a group of controls (49 treated with commercially available silymarin, 117 untreated or given placebo)²².

Studies have shown ginkgo phytosome (prepared from the standardized extract of *Ginkgo biloba* leaves) produced better results compared to the conventional standardized extract from the plant (GBE, 24 % ginkgo flavone glycoside and 6 % terpene lactones). In a bioavailability study conducted with healthy human volunteers

the levels of GBE constituents (flavonoids and terpenes) from the phytosomal form peaked after 3 hours and persisted longer for at least 5 hours after oral administration. It was found that the phytosomal GBE produced a 2-4 times greater plasma concentration of terpenes than did the non-phytosomal GBE. Its major indications are cerebral insufficiency and peripheral vascular disorders, and it also can ameliorate reduced cerebral circulation. Its improved oral bioavailability and good tolerability makes it the ideal Ginkgo product even for long term treatment. In studies with ginkgo phytosome in patients with peripheral vascular disease (e.g. Raynaud's disease and intermittent circulation) it was shown to produce a 30-60 % greater improvement compared to regular standardized GBE^{7,23}.

Grape seed phytosome is composed of oligomeric polyphenols (grape proanthocyanidins or procyanidins from grape seed extract, *Vitis vinifera*) of varying molecular size, complexed with phospholipids. The main properties of procyanidin flavonoids of grape seed are an increase in total antioxidant capacity and stimulation of physiological antioxidant defenses of plasma, protection against ischemia/reperfusion induced damages in the heart, protective effects against atherosclerosis thereby offering marked protection for the cardiovascular system and other organs through a network of mechanisms that extend beyond their great antioxidant potency²⁴.

In a study where rabbits were fed a high cholesterol diet for 6 weeks, to markedly elevate 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 extract²⁵.

Green tea extract generally contains a totally standardized polyphenolic fraction (not less than 66.5 %, containing epigallocatechin and its derivatives) 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. Green tea has got several long term beneficial activities such as antioxidant, anticarcinogenic, antimutagenic, antiatherosclerotic, hypocholesterolemic, cardioprotective, antibacterial and anticariogenic effects. 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 non complexed green tea extract following oral administration. Over the study period of 6 hours the plasma concentration of total flavonoids was more than doubled when coming from the phytosomal versus the non-phytosomal 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^{7,26}.

Maiti et al. developed the quercetin-phospholipid phytosomal complex by a

Table 1: Commercial phytosome products^{6, 7, 23}

S/N	Phytosomes	Phytoconstituents complexed	Dose	Indications
1	Silybin Phytosome™	Silybin from <i>Silybum marianum</i>	120 mg	Hepatoprotective, antioxidant for liver and skin
2	Ginkgo Phytosome™	24 % ginkgo flavonoids from <i>Ginkgo biloba</i>	120 mg	Protects brain and vascular linings, anti-skin ageing
3	Ginseng Phytosome™	37.5 % ginsenosides from <i>Panax ginseng</i>	150 mg	Nutraceutical, immunomodulator
4	Green Tea Phytosome™	Epigallocatechin from <i>Thea sinensis</i>	50-100 mg	Nutraceutical, systemic antioxidant, anti-cancer
5	Grape Seed Phytosome™	Procyanidins from <i>Vitis vinifera</i>	50-100 mg	Nutraceutical, systemic antioxidant, cardio-protective.
6	Hawthorn Phytosome™	Flavonoids from <i>Crataegus sp.</i>	100 mg	Nutraceutical, cardio-protective and antihypertensive
7	Olive oil Phytosome	Polyphenols from <i>Olea europaea</i> oil	-	Antioxidant, anti-inflammatory, anti-hyperlipidemic
8	Echinacea Phytosome	Echinacosides from <i>Echinacea angustifolia</i>	-	Nutraceutical, immunomodulator

simple and reproducible method and also showed that the formulation exerted better therapeutic efficacy than the molecule in rat liver injury induced by carbon tetrachloride²⁷.

Recently Maiti et al. developed the phytosomes of curcumin (flavonoid from turmeric, *Curcuma longa*) and naringenin (flavonoid from grape fruit, *Vitis vinifera*) in two different studies^{10,11}. The antioxidant activity of the complex was significantly higher than pure curcumin in all dose levels tested. In the other study the developed phytosome of naringenin produced better antioxidant activity than the free compound with a prolonged duration of action, which may be due to decrease in the rapid elimination of the molecule from body.

In this way different phytosome products (Table 1) have demonstrated significant therapeutic or health giving effects when compared with the conventional plant extracts.

Conclusion

In recent times the emerging technology of drug delivery and drug targeting is also being applied to phytopharmaceuticals. Botanicals have enormous therapeutic potential which should be explored through some value added drug delivery systems. Standardized plant extracts or mainly polar phytoconstituents like flavonoids, terpenoids, tannins, xanthenes when complexed with phospholipids like phosphatidylcholine give rise to a new drug delivery technology called phytosome showing much better absorption profile following oral administration owing to improved lipid solubility which enables them to cross the biological membrane, resulting enhanced bioavailability i.e. more amount of active principle in the systemic circulation. This means more amount of active constituent becomes present at the site of action (liver, brain, heart, kidney etc) at similar or less dose as compared to the conventional plant extract. Hence, the therapeutic action becomes enhanced, more

detectable and prolonged. Several excellent phytoconstituents have been successfully delivered in this way exhibiting remarkable therapeutic efficacy in animal as well as in human models. Recently Mukherjee et al. has regarded phytosomes as a value added drug delivery system²⁸.

Thorough study of literature reveals that several plant extracts (crude, partially purified or fractionated) are reported to possess different significant pharmacological or health promoting properties. These extracts can be standardized accordingly and may be formulated as phytosomes for systematic investigation for any improved potential to be used rationally. In this way after screening and selection of potential extracts or constituents from plants, phytosomes can be developed for different therapeutic purposes like cardiovascular, anti-inflammatory, immunomodulator, anticancer, antidiabetic etc or for prophylactic and health purposes as nutraceuticals, in due course.

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