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## PHYTOSOME: A NOVEL DRUG DELIVERY SYSTEM FOR IMPROVING BIOAVAILABILITY OF HERBAL MEDICINE

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### ABSTRACT

The term “Phyto” means plant while “some” means cell-like. Phytosomes are little cell like structure. Phytosome is a novel forms of herbal formulations which contains the bioactive phytoconstituents of herb extract surrounds and bound by a lipid. Most of the bioactive phytoconstituents are water-soluble compounds like flavonoids, glycosides; terpenoids shows less absorption. Due to water soluble herbal extract and lipophilic outer layer phytosomes shows better absorption and as a result produce better bioavailability and actions than the conventional herbal extracts containing dosage form. Phytosomes are produced by a process where by 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 enhance 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.

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### Key Words

Phytosomes, Phospholipids,  
Phosphatidylcholine,  
Bioavailability.

## INTRODUCTION

The advancement in the field of herbal drug delivery started recently with the aim to manage human diseases efficiently. Every nation is seeking health care beyond the traditional boundaries of modern medicine; turning to self medication in the form of herbal remedies<sup>[1,2]</sup>.

Nowadays expensive research in novel drug delivery systems is going on to improve the therapeutic efficacy of the existing natural molecules. Toxicity and limited absorption of different phytoconstituents obtained from herbs are major problems in exploring their real potentials against different diseases. So, extensive research in the field of herbal drug delivery systems as a means of improving the therapeutic indices of drugs is inevitable.

During the last century, chemical and pharmacological studies have been performed on a lot of plant extracts in order to know their chemical composition and confirm the indications of traditional medicine.

The Phytosome process produces a little cell because of that the valuable components of the herbal extract are protected from destruction by digestive secretions and gut bacteria. Phytosomes are better able to transition from a hydrophilic environment into the lipid-friendly environment of the enterocyte cell membrane and from there into the cell, finally reaching the blood<sup>[3]</sup>.

Most of the bioactive constituents of phytomedicines are flavonoids (e.g., anthocyanidins from bilberry, catechins from green tea, silymarin from milk thistle). However, many flavonoids are poorly absorbed; the poor absorption of flavonoid nutrients is likely due to two factors. First, they are having multiple-ring molecules that are too large to be absorbed by simple diffusion. Secondly, flavonoid molecules typically have poor miscibility with oils and other lipids, which limited their ability to pass across the lipid-rich outer membranes of the enterocytes of the small intestine. Watersoluble flavonoid molecules can be converted into lipid-compatible molecular complexes; aptly called phytosomes.

The term “phyto” means plant while “some” means cell like<sup>[4]</sup>. Phytosome is a newly introduced patented technology developed to incorporate standardized plant

extracts or water soluble phytoconstituents into phospholipids to produce lipid compatible molecular complexes, called as phytosomes (also often referred as herbosome in certain literature) and so vastly improve their absorption and bioavailability<sup>[5]</sup>. The lipid-phase substances employed to make flavonoids lipid-compatible are phospholipids from soy, mainly phosphatidylcholine.

Phosphatidylcholine(PC) is the principal molecular building block of cell membranes miscible both in water and in oil environments, and is well absorbed when taken by mouth. Chemical analysis indicates that the phytosome is usually a flavonoid molecule linked with at least one phosphatidylcholine molecule. A bond is formed between these two molecules, creating a hybrid molecule. This highly lipid-miscible hybrid bond is better suited to merge into the lipid phase of the enterocyte's outer cell membrane. Phosphatidylcholine is not merely a passive "carrier" for the bioactive flavonoids of the phytosomes, but is itself a bioactive nutrient with documented clinical efficacy for liver disease, including alcoholic hepatic steatosis, drug-induced liver damage, and hepatitis. 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. Specifically, the choline head of the phosphatidylcholine molecule binds to these compounds while the fat-soluble phosphatidyl portion comprising the body and tail then envelopes the choline-bound material. The result is a little microsphere or cell like structure<sup>[2]</sup>.

Phytosomes have improved pharmacokinetic and pharmacological parameters, which in result can advantageously be used in the treatment of acute and chronic liver disease of toxic metabolic or infective origin or of degenerative nature. It can also be used in anti-inflammatory activity as well as in pharmaceutical and cosmetic compositions<sup>[6]</sup>. PC is miscible both in the water phase and in oil/lipid phases, and is excellently absorbed when taken by mouth. PC is the principal molecular building block for cell membranes [Fig. 1], and

the molecular properties that suit PC for this role also render it close to ideal for its phytosome role.

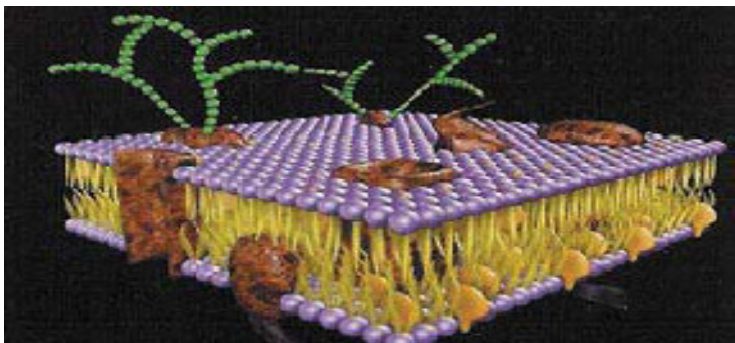


Fig. 1: Cell membranes are largely lipid

phase.

A double molecular layer consisting of PC and other phospholipids provides a continuous matrix into which the proteins insert

### ADVANTAGES OF PHYTOSOMES

1. Marked enhancement of bioavailability.
2. Phytosome process produces a little cell whereby the valuable components of the herbal extracts are protected from destruction by digestive secretions and gut bacteria.
3. Assured delivery to the tissues.
4. No compromise of nutrient safety.
5. Dose requirement is reduced due to absorption of chief constituent.
6. Entrapment efficiency is high and more over predetermined because drug itself in conjugation with lipids is forming vesicles.
7. No problem of drug entrapment.
8. Phytosomes shows better stability profile because chemical bonds are formed between phosphatidylcholine molecules and phytoconstituent.
9. Phosphatidylcholine used in the phytosome process besides acting as a carrier also nourishes the skin, because it is essential part of cell membrane.
10. Phytosomes are also superior to liposomes in skin care products.
11. Significantly greater clinical benefit.
12. The particular structure of phytosome elicits peculiar properties and advantages in cosmetic application.
13. Enhanced ability of phytosomes to cross cell membranes and enter cells.

14. Their low solubility in aqueous media allows the formation of stable emulsions or creams.

### PROPERTIES OF PHYTOSOMES

#### Physico Chemical properties

Phytosomes is a complex between a natural product and natural phospholipids, like soy phospholipids. Such a complex is obtained by reaction of stoichiometric amounts of phospholipids and the substrate in an appropriate solvent. On the basis of spectroscopic data it has been shown that the main phospholipids-substrate interaction 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 treated with water, phytosomes assumes a micellar shape forming liposomal-like structures.

In liposomes the active principle is dissolved in the internal pocket or it 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 catechindistearoylphosphatidylcholine complex, there is the formation of H-bonds between the phenolic hydroxyl ends of the flavones moiety and the phosphate ion on the phosphatidylcholine moiety. Phosphatidyl choline can be deduced from the comparison of  $^1\text{H-NMR}$  and  $^{13}\text{C-NMR}$  spectra of the complex with those of the pure precursors. The signals of fatty chain remain almost unchanged. Such evidence inferred that the too long aliphatic chains are wrapped around the active principle, producing a lipophilic envelope, which shields the polar head of the phospholipid and flavanoid molecule and enables the complex to dissolve in low polarity solvents<sup>[6,7]</sup>.

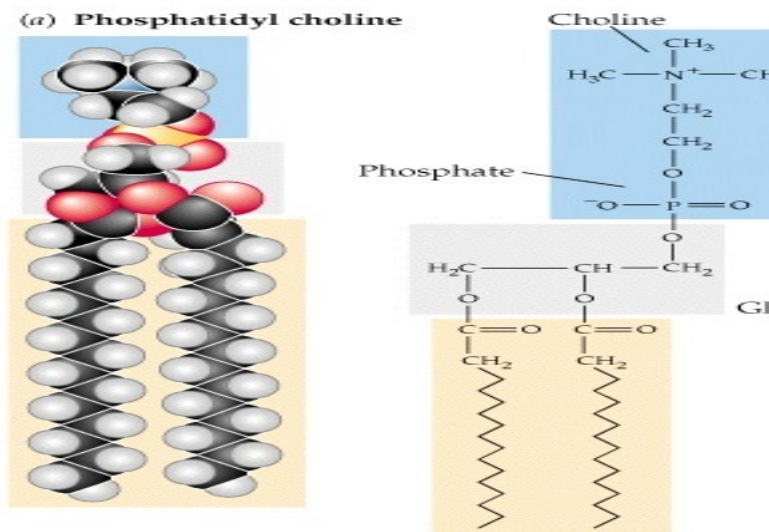


Figure 2. Structure of Phosphatidyl choline(PC)

## PHARMACOLOGICAL

Phytosomes are advanced forms of herbal products that are better absorbed, utilized and as a result produce better results than conventional herbal extracts. The increased bioavailability of the phytosome over the non complexed botanical derivatives has been demonstrated by pharmacokinetic studies or by pharmacodynamic tests in experimental animals and in human subjects<sup>[8]</sup>.

## CHARACTERIZATION OF PHYTOSOMES

The behaviour of phytosomes in both physical and biological system is governed by the factors such as physical size, membrane permeability, percentage of 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 release and chemical composition<sup>[9]</sup>.

## DIFFERENT CHARACTERIZATION TECHNIQUES USED FOR PHYTOSOMES

### VISUALIZATION

Visualization of phytosomes can be achieved using transmission electron microscopy (TEM) and by scanning electron microscopy (SEM)<sup>[10]</sup>.

### VESICLE SIZE AND ZETA POTENTIAL

The particle size and zeta potential can be determined by dynamic light scattering (DLS) using a computerized inspection system and photon correlation spectroscopy (PCS)<sup>[11]</sup>.

### ENTRAPMENT EFFICIENCY

The entrapment efficiency of a drug by phytosomes can be measured by the ultracentrifugation technique<sup>[12]</sup>.

### TRANSITION TEMPERATURE

The transition temperature of the vesicular lipid systems can be determined by differential scanning calorimetry<sup>[13]</sup>.

### SURFACE TENSION ACTIVITY MEASUREMENT

The surface tension activity of the drug in aqueous solution can be measured by the ring method in a Du Nouy ring tensiometer<sup>[14]</sup>.

### VESICLE STABILITY

The stability of vesicles can be determined by assessing the size and structure of the vesicles over time. The mean size is measured by DLS and structural changes are monitored by TEM<sup>[15]</sup>.

### DRUG CONTENT

The amount of drug can be quantified by a modified high performance liquid chromatographic method or by a suitable spectroscopic method<sup>[16]</sup>.

### SPECTROSCOPIC EVALUATIONS

To confirm the formation of a complex or to study the reciprocal interaction between the phytoconstituent and the phospholipids, the following spectroscopic methods are used<sup>[17]</sup>.

**1H-NMR**

The NMR spectra of (+)-catechin and its stoichiometric complex with distearoylphosphatidylcholine have been studied by Bombardelli et al [18]. In nonpolar solvents, there is a marked change of the <sup>1</sup>H-NMR signal originating from the atoms involved in the formation of the complex, without any summation of the signal peculiar to the individual molecules. The signals from the protons belonging to the flavonoids are to be broadened that the proton cannot be relieved. In phospholipids, there is broadening of all the signals while the singlet corresponding to the N-(CH<sub>3</sub>)<sub>3</sub> of choline undergoes an upfield shift. Heating the sample to 60° results in the appearance of some new broad bands, which correspond mainly to the resonance of the flavonoid moiety.

**C-NMR**

In the <sup>13</sup>C-NMR spectrum of (+)-catechin and its stoichiometric complex with distearoylphosphatidylcholine, particularly when recorded in C<sub>6</sub>D<sub>6</sub> at room temperature, all the flavonoid carbons are clearly invisible. The signals corresponding to the glycerol and choline portion of the lipid (between 60–80 ppm) are broadened and some are shifted, while most of the resonances of the fatty acid chains retain their original sharp line shape. After heating to 60°, all the signals belonging to the flavonoid moieties reappear, although they are still very broad and partially overlapping.

**FTIR**

The formation of the complex can be also be confirmed by IR spectroscopy by comparing the spectrum of the complex with the spectrum of the individual components and their mechanical mixtures. FTIR spectroscopy is also a useful tool for the control of the stability of phytosomes when micro-dispersed in water or when incorporated in very simple cosmetic gels. From a practical point of view, the stability can be confirmed by comparing the spectrum of the complex in solid form (phytosomes) with the spectrum of its micro-dispersion

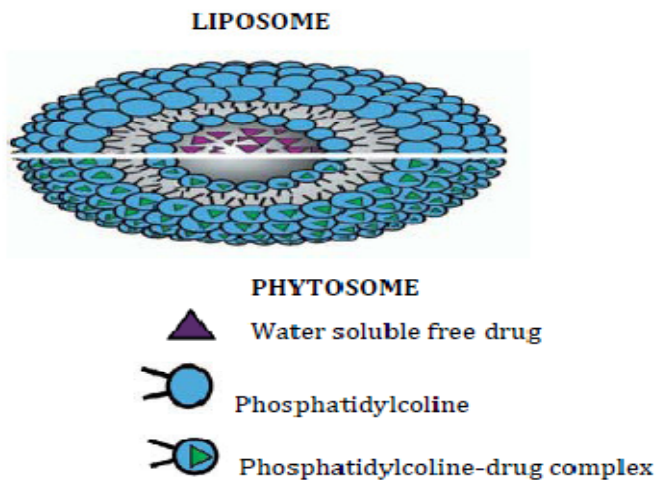
in water after lyophilization, at different times. In the case of simple formulations, it is necessary to subtract the spectrum of the excipients (blank) from the spectrum of the cosmetic form at different times, comparing the remaining spectrum of the complex itself. 5.3. In vitro and in vivo evaluations Models of in-vitro and in-vivo evaluations are selected on the basis of the expected therapeutic activity of the biologically active phytoconstituents present in the phytosomes [17]. For example, in-vitro antihepatotoxic activity can be assessed by the antioxidant and free radical scavenging activity of the phytosomes. For assessing antihepatotoxic activity in-vivo, the effect of prepared phytosomes on animals against thioacetamide-, paracetamol alcohol- induced hepatotoxicity can be examined [19-20]. Skin sensitization and tolerability studies of glycyrrhetic acid-Phytosome® ointment, a commercial product, describe the in vivo safety evaluation methodology [21]. Filburn et al. studied the bioavailability of a silybinphosphatidylcholine complex in dog models to examine the pharmacokinetic parameters of this new complexed form [22].

**DIFFERENCE BETWEEN PHYTOSOME AND LIPOSOME**

Primarily liposomes are used in cosmetics to deliver water-soluble substances to the skin. It is formed by mixing a water-soluble substance with phosphatidylcholine. No chemical bond is formed. There may be hundreds or even thousands of phosphatidylcholine molecules surrounding the water-soluble compound. In contrast, with the phytosomes process the phosphatidylcholine and the individual plant components actually form a 1:1 or a 2:1 complex depending on the substance. This difference results in phytosome being much better absorbed than liposomes, showing better bioavailability. Liposomes have also been found inferior to phytosomes in topical and skin care (cosmetic) products.

Phytosomes operate with the solvent having a reduced dielectric constant where as liposome drugs complex operate in the presence of the water or buffer solution. Liposomes are touted delivery vehicles, but for dietary supplements their promise has not been fulfilled. On the other hand, phytosome products were proven to have

better absorption and substantially greater clinical efficacy.



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

## METHOD OF PREPARATION

Phytosomes are prepared by reacting natural or synthetic phospholipids with active components like bioflavonoid, flavolignan and polyphenolic constituents. Solvent Evaporation method is used for the preparation of ginsenoside, puerarin and kushenin are prepared in this manner. Mechanical Dispersion method is used for the preparation of marsupin-phospholipid complexes. Phospholipids is dissolved in a suitable solvent and active ingredient is added drop by drop while sonicating the solution. Phospholipid complex is sometimes prepared under reflux and stirring conditions to effect complete interaction. Curcumin phospholipids complexes are prepared by adding the phospholipids to the ethanol solution of the hydroalcoholic extract of turmeric rhizomes, under reflux and with stirring. Prepared complex called phytosome can be isolated by precipitation with nonsolvent, lyophilization, spray drying or vacuum drying<sup>[23-32]</sup>.

## APPLICATIONS OF PHYTOSOMES

Most of the phytosomal studies are focused to *Silybum marianum* which contains premier liver-protectant flavonoids. The fruit of the milk thistle plant (*S. marianum*, Family *Steraceae*) contains flavonoids known for hepatoprotective effects. Silymarin has been shown

to have positive effects in treating liver diseases of various kinds, including hepatitis, cirrhosis, fatty infiltration of the liver (chemical and alcohol induced fatty liver) and inflammation of the bile duct. The antioxidant capacity of silymarin substantially boosts the liver's resistance to toxic insults<sup>[33]</sup>.

Silymarin primarily contains three flavonoids of the flavonol subclass (having a fully saturated C-ring). Silybin predominates, followed by silydianin and silychristin. Silybin is actually a flavonolignan, 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<sup>[34]</sup>. Silybin protects the liver by conserving glutathione in the parenchymal cells<sup>[33]</sup>, while PC helps repair and replace cell membranes<sup>[35]</sup>. These constituents likely 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.

Francesco *et al.*, (2009) studied on a recently developed oral formulation in the form of coated tablets (Monoselect Camellia®) (MonCam) containing highly bioavailable green tea extract (GreenSelect® Phytosome) was tested in obese subjects (n=100) of both genders on a hypocaloric diet. Fifty subjects were assigned to the green tea extract plus hypocaloric diet, while the other 50 subjects followed the hypocaloric diet only. After 90 days of treatment, significant weight loss and decreased body mass index (BMI) were observed in the group taking the herbal extract (14 kg loss in the green tea group compared to a 5 kg loss in the diet-only group); waistline was reduced only in male subjects. Besides the effect on weight and BMI, biochemical parameters (LDL, HDL, and total cholesterol, triglycerides, growth hormone, insulin-like growth factor-1, insulin, and cortisol) were improved in both groups. Leptin, not tested in the diet-only group, was reduced in patients taking MonCam. Taking into consideration the high safety profile of the product and the total absence of adverse effects observed during

and after the trial, MonCam appears to be a safe and effective tool for weight loss<sup>[36]</sup>.

Mukerjee *et al.*, (2008) developed a novel hesperetin phytosome by complexing hesperetin with hydrogenated phosphatidyl choline. This complex was then evaluated for antioxidant activity in CCl<sub>4</sub> intoxicated rats along with pharmacokinetic studies. It was found that the phytosome had a sustained release property for over 24 h and enhanced antioxidant activity. Pharmacokinetic study revealed that the phytosome had higher relative bioavailability than that of parent molecule at the same dose level<sup>[37]</sup>.

Yanyu *et al.*, (2006) 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 silybin<sup>[38]</sup>.

Ravarotto *et al.*, (2004) reported silymarin phytosome show better antihepatotoxic activity than silymarin alone and can provide protection against the toxic effects of aflatoxin B1 on performance of broiler chicks<sup>[39]</sup>.

Busby *et al.*, (2002) reported that the use of a silymarin phytosome showed a better fetoprotectant activity from ethanol-induced behavioral deficits than uncomplexed silymarin<sup>[40]</sup>.

Bombardelli *et al.*, (1991) 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 components, with respect to per cent reduction of edema, inhibition of myeloperoxidase activity, antioxidant and free radical scavenging properties<sup>[41]</sup>.

Aiti *et al.*, (2005) developed the quercetin-phospholipids complex by a simple and reproducible method and also showed that the formulation exerted better therapeutic efficacy than the molecule in rat liver injury induced by carbon tetrachloride<sup>[42]</sup>.

Barzaghi *et al.*, (1990) 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)<sup>[43]</sup>.

Moscarella *et al.*, (1993) 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)<sup>[44]</sup>.

Grange *et al.*, (1999) 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 ethanol. [29] 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 potency. [30] 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, cardio-protective, 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

**Table 1:** Commercial Phytosome Products [6, 47,48]

S. No.	Phytosomes	Phytoconstituents complexed	Dose *	Indications
1.	Silybin Phytosome™	Silybin from <i>Silybum marianum</i>	120 mg	Hepatoprotective, antioxidant for liver
2.	Ginkgo Phytosome™ 24 %	Ginkgo flavonoids from <i>Ginkgo biloba</i>	120 mg	Protects brain and vascular linings
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, anticancer
5.	Grape Seed Phytosome™	Procyanidins from <i>Vitis vinifera</i>	50-100 mg	systemic antioxidant, cardio-protective
6.	Hawthorn Phytosome™	Flavonoids from <i>Crataegus sp.</i>	100 mg	cardio-protective and antihypertensive
7.	Olive oil Phytosome	Polyphenols from <i>Olea europaea</i> oil	-	anti-inflammatory, anti-hyperlipidemic
8.	Echinacea Phytosome	Echinacosides from <i>Echinacea augustifolia</i>	-	Nutraceutical, immunomodulator
9.	Centella Phytosome	Terpenes	-	Vein and Skin disorders
10.	Palmetto berries Phytosomes	Fatty acids, alcohols and sterols	-	Non-cancerous prostate enlargement
11.	Super Milk thistle Extract	Silybin from Silymarin Food Product	-	antioxidant for liver and skin
12.	Bilberry Phytosomes	Extract of bilberry	-	Improve capillary tone, antioxidants.

Phytosomes are advanced form of herbal extract that are better absorbed which results better than conventional herbal extract. Phytosomes have improved pharmacokinetic and pharmacological parameter, which in result can advantageously be used in treatment of acute liver diseases, either metabolic or infective origin. Absorption of phytosome in gastro-intestinal tract is appreciably greater resulting in increased plasma level than the individual component. 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. Thorough study of

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 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<sup>[45-46]</sup>.

Commercial product of phytosomes prepared from herbs available in market is shown in Table 1.

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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