PHYTOSOMES AN EMERGING TECHNOLOGY FOR HERBAL DRUG DELIVERY: AN APPROACH TO HEPATOPROTECTION

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ABSTRACT
Phytoconstituents, despite having excellent bioactivity in vitro, demonstrate less or no in vivo actions due to their poor lipid solubility or improper molecular size or both, resulting in poor absorption and poor bioavailability. Lipid solubility and molecular size are the major limiting factors for molecules to pass the biological membrane and to be absorbed systematically following oral or topical administration. Some phytoconstituents are destroyed in the gastric environment when taken orally. The term “phyto” means plant, while “some” means cell-like. Therefore, phytosome is a “phytophospholipid complex” resembling a small cell. Phytosomes are produced by a patented process whereby standardized plant extracts or their constituents are bound to phospholipids, mainly phosphatidylcholine, producing a lipid-compatible molecular complex. Phytosomes exhibit a better pharmacokinetic and pharmacodynamic profile than conventional herbal extracts. The phytosome technology markedly enhances the bioavailability of phytomedicine and has effectively 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. The focus of this review is to elucidate the concept of hepatotoxicity, including its causes, pathogenesis and prevention. The article also reviews the scope of herbal plants as well as novel delivery systems like phytosomes for the treatment of hepatotoxicity and liver related disorders. It has a lot of potential in the field of medicine, pharmaceuticals and cosmetics.

Key words: Drug delivery, phosphatidylcholine, phytoconstituents, hepatotoxicity, Herbal.
INTRODUCTION
Medicinal plants have been acknowledged and are extremely valued all over the world as a prosperous source of bioactives for the prevention and treatment of ailments. Herbal medicines are being used by about 80% of the world population primarily in the developing countries for primary health care. They have stood the test of time for their safety, efficacy, cultural acceptability and minimal side effects, liver an imperative organ has a crucial in the metabolism of xenobiotics that causes it to succumb to numerous hepatic diseases. Synthetic drugs exploited in the treatment of liver diseases are incompetent and may sometimes lead to serious side-effects. In this context, herbal therapy has emerged as a proficient approach with good values in treating hepatic diseases.\textsuperscript{1, 2} developing a satisfactory herbal therapy to treat severe liver diseases requires systematic investigation of properties such as antiviral action (hepatitis b, hepatitis c), anti-hepatotoxicity (antioxidants), stimulation of liver regeneration and choleretic activity. The focus of this review is to elucidate the concept of hepatotoxicity, including its causes, pathogenesis and prevention. The article also reviews the scope of herbal plants as well as novel delivery systems like phytosomes for the treatment of hepatotoxicity and liver related disorders. medicinal herbs are significant source of hepatoprotective drugs. It has been reported that about 170 phytoconstituents isolated from 110 plants belonging to 55 families do possess hepatoprotective activity liver protective herbal drugs contain a variety of chemical constituents like phenols, coumarins, curcuminoids, lignans, essential oils and terpenoids.\textsuperscript{3, 4} The phytosomes hasmore ability to carry the herbal extract of hydrophilic nature through the lipid bilayer and thus it is more bioavailable compared to simple extract. The phytosome technology has been reported to effectively enhance the bioavailability of many popular herbal extracts including milk thistle, ginkgo biloba, grape seed, green tea, hawthorn, ginseng turmeric, centella, ammi etc and can further be developed for various therapeutic uses or dietary supplements. The focus of this review is to elucidate the concept of hepatotoxicity, novel delivery systems like phytosomes for the treatment of hepatotoxicity and liver related disorders. Including its causes, pathogenesis and prevention.\textsuperscript{5, 6}

PHOSPHATIDYLCHOLINE AND HERBAL EXTRACT
Phospholipids are a class of lipids and are a major component of all cell membrane. 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 a major component of biological membrane and can be isolated from either egg yolk or soy beans from which they are mechanically extracted or chemically extracted using hexane.
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 the components of herbal extract while the lipid soluble phosphatidyl portion then envelopes the choline bound material that results in a little micro sphere or cell is produced. The term "phyto" means plant while "some" means cell-like. What the Phytosome process produces is a microsphere cell that protects valuable components of the herbal extract from destruction by digestive secretions and gut bacteria.\textsuperscript{6, 7, 8}

Figure 1. Structure of Phosphatidylcholine (PC)

Many popular standardized herbal extracts comprising of flavanoids, polyphenolics, terpenes, alkaloids, volatile oils are employed for the preparation of phytosomes. The hypothesis of an interaction with phospholipids originated from a histochemical finding indicating that anthocyanosides from \textit{Vaccinium myrtillus} L. showed a strong affinity for specific cellular structures rich in phospholipids. Evidence that flavonoids as well as saponins and triterpenic acids, do form real complexes with phospholipids was obtained about years ago when these complexes could be prepared and chemically standardized. Mainly flavanoids and polyphenolics are complexed with the phospholipids molecules and forms phytosomes. More than 4,000 naturally occurring flavonoids have been identified, each with its own distinctive molecular structure and 3-D shape. Flavonoids are part of a broader class of dietary antioxidants called polyphenols and are distinctive for their triple ring structures.\textsuperscript{9, 10} the poor absorption of polyphenolics is likely due to two main factors. First, these are multiple-ring molecules not quite small enough to be absorbed from the intestine into the blood by simple diffusion nor does the intestinal lining actively absorb them, as occurs with some vitamins
and minerals. Second, they typically have poor miscibility with oils and other lipids. This severely limits their ability to pass across the lipid-rich outer membranes of the enterocytes, the cells that line the small intestine. PC is miscible both in the water phase and in oil/lipid phases, and is excellently absorbed when taken by mouth. The molecular properties of PC and precise chemical analysis indicate the unit phytosome is usually a herbal extract molecule linked with at least one PC molecule. A bond is formed between the two molecules to create a hybrid molecule. This hybrid is highly lipid-miscible, better suited to merge into the lipid phase of the enterocyte’s outer cell membrane. Once there, it can cross the enterocyte and reach the circulating blood.\textsuperscript{11, 12}

![Figure 2. Hepatotoxicity and its mechanism](image)

![Figure 3. Role of hepatotoxic mediators and hepatoprotective mediators](image)
Herbal plant used for hepato-protective \(^8,9\)

![Image of plants](image1)

- **Andrographis paniculata** (Acanthaceae) Aerial part andrographolide (flavonoid)
- **Azadirachta indica** (Meliaceae) Aerial parts Azadirachta, margarolise
- **Allium sativum** (Liliaceae) Bulb Allium, sativum
- **Camellia sinensis** (Theaceae) leaves catechins epigallocatechin
gallate.

**Figure 4.** Structure of hepatoprotective plant

- Paracetamol induced toxicity
- Administered less than plasma ALT and ALP activities increased
- CCA4 and acetaminophen extract induced toxicities on HepG2 cell lines and apo extract to exert a Cholesteric effect that reduced the cholesterol and increase the excretion of toxic xenobiotic from liver.

- Azadirachta administered enhanced the hepatic level of glutathione dependent enzymes like GPX from protein. The results suggest that the hepatoprotective as well as antioxidant properties have the ability to have antioxidant properties and to stabilize cell membranes reduction in serum hepatic enzymes and liver lipid peroxide which were increased by carbon tetrachloride.

- Administered camilla

- CD4 damage by estimating level of Marker enzyme (AST ALT, ALP) total protein, Alb in serum controlled (ginko) biloba.

**Figure 5.** Structure of hepatoprotective plants \(^8,9,10\)
Carrier systems for herbal drug

Delivery in liver

Drug delivery is a preliminary requirement. Emphasis needs to be laid in developing vehicles that can transport bioactives to the liver with reduced access to non-specific tissues.

Phytosomes

Phospholipids are complex molecules used in all known life forms to build cell membranes. The term “phyto” implies plant while “some” means cell-like. Water-soluble phytocomponents molecules (mainly polyphenoles) can be converted into lipid-compatible molecular complexes, which are called phytosomes. Phytosomes may augment bioavailability as compared to simple herbal extracts owing to their enhanced capacity to cross the lipid rich biomembranes and finally enter the systemic circulation the blood. Phytosomes are better able to transit a hydrophilic environment into the lipid-friendly environment of the enterocyte cell membrane and from there into the cell, finally reaching the blood. Chemical analysis indicates that in 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. The phytosomal preparations that have been demonstrated safe and effective in live. \(^{11,12,13}\)

Figure 6. Structure of Phytosomes
PREPARATION OF PHYTOSOME- THE PHYTOSOME TECHNOLOGY

1. Phytosomes are novel complexes which are prepared by reacting from 3-2 moles but preferably with one mole of a natural or synthetic phospholipid, such as phosphatidylcholine, phosphatidylethanolamine or phosphatidyserine with one mole of component for example- flavolignans, 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 phospholipid to flavonoids is 1:1.

2. Naringenin–pc complex was prepared by taking naringenin with an equimolar concentration of phosphatidylcholine (pc). The equimolar concentration of pc and naringenin were placed in a 100 ml round bottom flask and refluxed in dichloromethane for 3 h. On concentrating the solution to 5–10 ml, 30 ml of n-hexane was added to get the complex as a precipitate followed by filtration. The precipitate was collected and placed in vacuum desiccators.

3. The required amounts of drug and phospholipids were placed in a 100 ml round-bottom flask and dissolved in anhydrous ethanol. After ethanol was evaporated off under vacuum at 40 °c, the dried residues were gathered and placed in desiccators overnight, then crushed in the mortar and sieved with a 100 mesh. The resultant silybin-phospholipid complex was transferred into a glass bottle, flushed with nitrogen and stored in the room temperature.

4. The flavonoid and terpenoid constituents of plant extracts lend themselves quite well for the direct binding to phosphatidylcholine. Phytosomes results from the reaction of stoichiometric amount of the phospholipid (phosphatidylcholine) with the standardized extract or polyphenolic constituents (like simple flavonoids) in a non polar solvent. 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.
Phospholipids dissolved in organic solvent containing Drug/extract
step 2

Drying of solution of phospholipids in organic solvent
With drug/extract

Step 3

formation of thin film

Step 4

Hydration of thin film

Step 5

Formation of phytosomal suspension

Improved Bioavailability Of Herbal Extract With Improved

RESULTS
The phytosome process has been applied to many popular herbal extracts including Ginkgo biloba, grape seed, hawthorn, milk thistle, green tea, and ginseng and recent research shows improved absorption and bioavailability with phytosomes as compared to the conventional means. Many standardized extract containing flavanoids and polyphenolics have been reported with improved bioavailability when incorporated in photosomal preparation. Silymarin is some of the most studied drug for the better delivery of silybin by forming silybin-phospholipid complex. 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 due to an improvement of the lipophilic property of silybin-phospholipid complex.\textsuperscript{15,16}

Siliphos milk thistle phytosome
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. Silymarin phytosomes studied for its pharmacokinetics in rats and bioavailability of silybin in rats was remarkably increased after oral administration of prepared silybin-phospholipid complex possibly due to improved
lipophilic property of silybin-phospholipid complex and subsequent biological effect of silybin. In a similar study demonstrated that silymarin phytosome exerted a better antihepatotoxic activity than silymarin alone and provided protection against the toxic effects of aflatoxin on performance of broiler chicks. Silymarin phytosomes, in which silymarin (a standardized mixture of flavanolignans extracted from the fruits of S. Marianum) was complexed with phospholipids showed much higher specific activity and a longer lasting action than the single constituent, with respect to percent reduction of edema, inhibition of myeloperoxidase activity, antioxidant and free radical scavenging properties.

Ginkgoselect phytosome
Ginkgoselect phytosomes (gsp) were prepared via complexation of ginkgo biloba extract with soy phospholipids (1:2 w/w). Liver damage was induced in wistar rats by administering rifampicin simultaneously and gsp were administered orally for 30 days/daily to rmp treated rats. Level of marker enzymes (sgot, sgpt and salp), albumin (alb) and total proteins (tp) were assessed in serum. Treatments with gbp50 as well as silymarin decreased the sgot, sgpt and salp elevated by rmp and increased the alb and tp levels. Sgot and sgpt levels were nearly restored to normal in the gbp50 treated group.

Quercetin phytosomes
The quercetin-phospholipid phytosomal complex developed showed that the formulation exerted better therapeutic efficacy than the molecule in rat liver injury induced by carbon tetrachloride. Level of marker enzymes (sgot, sgpt and salp), albumin (alb) and total proteins (tp) were assessed in serum. Treatments with quercetin phytosomes decreased the sgot, sgpt and salp elevated by ccl4 and increased the alb and tp levels.

PROPERTIES OF PHYTOSOMES
Physico-chemical properties
- As previously discussed, phytosomes are prepared by reaction of stoichiometric amount of phospholipid with the standardized plant extract as substrate. The spectroscopic data reveals that the phospholipid-substrate interaction is due to the formation of hydrogen bond between the polar head (i.e., phosphate and ammonium group) and the polar functionalities of the substrate.
- The size of phytosome varies from 50 nm to a few hundred µm.
Phytosomes when treated with water, they assume a micellar shape resembling liposome and photon correlation spectroscopy (pcs) reveals these liposomal structures acquired by phytosomes.

Regarding the solubility of phytosomes, the complexes are often freely soluble in aprotic solvents, moderately soluble in fats, insoluble in water and relatively unstable in alcohol. But the phytosomes of certain lipophilic phytoconstituents like curcumin has shown increased water solubility upon complexation with phospholipids which has been discussed later in this paper.25,26,27

Biological properties
Phytosomes are novel complexes which are better absorbed and utilized; hence they produce more bioavailability and better result than the conventional herbal extract or non-complexed extracts, which has been demonstrated by pharmacokinetic studies or by pharmacodynamic tests in experimental animals and in human subjects28. Phytosomes express their behaviour in physical or biological system because of their physical size, membrane permeability, percentage entrapment, chemical composition, quantity and purity of the materials used. The phytosomes should not be confused with liposomes where hydrophilic drug molecules are entrapped within a cavity or spaces between the membranes. The liposomes may involve several hundred phospholipid molecules for this entrapment and are usually now being used for cosmetic purposes. Instead, the phytosomes involves interaction of 1-4 phospholipid molecules with the phytoconstituents which are chemically anchored to each other. Several researches have shown the phytosomes to be a better alternative for liposomes in terms of membrane permeability and stability. Fig.5 illustrates a comparative account of phytosomes with liposomes.28,29

Novel Approaches For Delivery Of Herbal Constituents
Liposomes
Liposomes are artificial microscopic vesicles consisting of an aqueous core enclosed in one or more phospholipid layers, used to convey vaccines, drugs, enzymes or other substances to target cells or organs.30,31

Nanoparticles
Nanoparticles are particles of less than 100nm in diameter that exhibit new or enhanced sizedependent properties compared with larger particles of same material.
Microemulsion
A thermodynamically stable dispersion of two immiscible liquids, stabilized by surfactants. A microemulsion is an emulsion whose particles are less than 1 micron in size.

Phytosome
It is a newly introduced patented technology developed to incorporate standardized plant extracts or water soluble phytoconstituents into phospholipids to produce lipid compatible molecular complexes they are also known as herbosome.\textsuperscript{32,33}

Transfersomes
A transfersomes carrier is an artificially designed to be like cell vesicle or a cell engaged in exocytosis and thus suitable for controlled and potentially targeted drug delivery. Transfersome consist of phosphatidylcholine and cholate and are ultra deformable vesicles with enhanced skin penetrating properties.\textsuperscript{34,35}

![Figure 7. organisation of phytosome complex](image)

Difference between phytosome and liposome the molecular organization of liposome upper segment the molecular organization of phytosome lower segment
Liposomes are prepared by same procedure as phytosomes. A liposome is formed by mixing a water soluble substance with phosphatidylcholine in definite ratio under specific conditions. The main differences between liposomes and phytomes are
1. Main difference is that in liposomes no chemical bond is formed and the phosphatidylcholine molecules surround the water soluble substance. In a liposome, the material is simply emulsified.

2. 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) complexes, involving chemical bonds. This difference results in better absorption of phytosomes than liposomes showing better bioavailability. Phytosomes have also been found superior to liposomes in topical and skin care products another difference is size of liposomes. Liposomes, although composed of phosphatidylcholine, are much larger.

3. Fundamental differences are that in liposomes, the active constituents are dissolved in the central part of the cavity, with no possibility of molecular interaction between the surrounding lipid and a hydrophilic substance. On the other hand the phytosome complex can somewhat be compared to an integral part of the lipid membrane, where the polar functionalities of the lipophilic molecule interact via hydrogen bonds with the polar head of a phospholipids (i.e. Phosphate and ammonium groups), forming a unique pattern which can be characterized by spectroscopy. This difference results in phytosome being much better absorbed than liposomes showing better bioavailability.

4. Phytosomes are also superior to liposomes in skin care products while the liposome is an aggregate of many phospholipids molecules that can enclose other phytoactive molecules but without specifically bonding to them.

5. Liposomes are touted delivery vehicles, but for dietary supplements, they are very less efficient. But for phytosome products numerous studies prove they are markedly better absorbed and have substantially greater clinical efficacy.

6. Some liposomal drug complexes operate in the presence of the water or buffer solution whereas phytosomes operate with the solvent having a reduced dielectric constant. Starting material of component like flavonoids 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.
Marketed Preparations Of Phytosomes

Silymarin phytosome
Most of the phytosomal studies are focused on silybum marianum (milk thistles) which contains premier liver protectant flavonoids. Yanyu et al. (2006) prepared silymarin phytosome and studies its pharmacokinetic in rats. In the studies, the bioavailability of silybin in rat was increased remarkably after oral administration of silybin-phospholipid complex due to an impressive improvement of the lipophilic properties of silybinphospholipid complex and improvement of biological effect of silybin. 39, 40

Curcumin phytosome
Maiti et al. (2006) developed the phytosomes of curcumin (flavonoid from curcuma longa, turmeric) and naringenin (flavonoid from grape fruit, vitis vinifera) in two different studies. The antioxidant activity of the complex was significantly higher than pure curcumin in all dose level 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 due to decrease in the rapid elimination of the molecule from body. 40, 41, 42

Evaluation Of Phytosomes

I. Characterization technique
1. Visualization: Visualization of phytosomes can be achieved using transmission electron microscopy (tem) and by scanning electron microscopy (sem). 42

2. Entrapment efficiency: The entrapment efficiency of a drug by phytosomes can be measured by the ultracentrifugation technique.

3. Transition temperature: The transition temperature of the vesicular lipid systems can be determined by differential scanning calorimetric. 43

4. 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 densitometer.

5. 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.
6. Drug content: The amount of drug can be quantified by a modified high performance liquid chromatographic method or by a suitable spectroscopic Method.

II. 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.

1. ^1^H NMR
2. ^13^C NMR
3. FTIR

Specific Agents And Their Effects On The Liver

Acetaminophen: Cytochrome p-450-2e1 generates a toxic metabolite napqi and this produces hepatic necrosis.

Amoxicillin: Moderate rise in sgot and sgpt level, hepatic dysfunction including jaundice, hepatic cholestasis and acute cytolytic hepatitis.

Chlorpromazine: Infectious hepatitis with laboratory features of obstructive jaundice.

Ciprofloxacin: Cholestatic jaundice, elevated sgpt, sgot and alkaline phosphatase level.

Diclofenac: Elevation of alt and ast level, liver necrosis, jaundice and fulminant hepatitis.

Erythromycin: Increased level of sgot, sgot, hepatocellular and/or cholestatic hepatitis with or without jaundice.

Fluconazole: Elevated transaminase level, hepatitis, cholestasis and fulminant hepatic failure.

Isoniazid: Elevation of serum transaminase level, severe and fatal hepatitis.

Phytosomes
Table 1: Marketed Preparations

<table>
<thead>
<tr>
<th>Phytosomes</th>
<th>Phytoconstituent complexed with phosphatidylcholine</th>
<th>Indication</th>
<th>Dose Mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Silybin phytosome Tm</td>
<td>Siybín from silymarin marínum</td>
<td>Nutraceutical, antioxidant</td>
<td>120</td>
</tr>
<tr>
<td>Ginkgo phytosome Tm</td>
<td>24% ginkgo flavonoids from Ginkgo biloba</td>
<td>Protects brain and vascular Lining</td>
<td>120</td>
</tr>
<tr>
<td>Green Tea Phytosome Tm</td>
<td>Epigallocatechin 3-o-gallate from Camellia sinensis</td>
<td>Anticancer, systemic Antioxidant</td>
<td>50-100</td>
</tr>
<tr>
<td>Olive oil Phytosomem</td>
<td>Poluphenols from olea europaea Oil</td>
<td>Anti-oxidant, anti inflammatory</td>
<td>-</td>
</tr>
<tr>
<td>Centella Phytosomem</td>
<td>Terpenes</td>
<td>Vein and skin disorders\textsuperscript{51}</td>
<td>-</td>
</tr>
</tbody>
</table>

CONCLUSION

Modern society has innate knowledge about the herbal treatment of liver disease from many cultures. Research into plants traditionally used in the treatment of liver disease has significantly advanced in the past 15 years, and much of what has been discovered supports traditional knowledge. There continues to be a need for safe, effective treatments of liver disease. An assortment of botanical medicines such as milk thistle, turmeric, green tea, licorice, tinospora cordifolia, andographis paniculata and picrorhiza, are the best-researched plants for the treatment of liver disease, with many human therapeutic trials available to the practicing physician to assess their potential effectiveness. Plant drugs (combinations or individual drug) for liver diseases should possess sufficient efficacy to cure severe liver diseases caused by toxic chemicals, viruses (hepatitis b, hepatitis c, etc.), excess alcohol intake, etc. A single drug cannot be effective against all types of severe liver diseases. Effective formulations have to be developed using indigenous medicinal plants, with proper pharmacological experiments and clinical trials. The manufacture of plant products should be governed by standards of safety and efficacy.

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