Research Article
Volume 15:1, 2023

Journal of Bioanalysis & Biomedicine

ISSN: 1948-593X Open Access

Phytosomes: Review on Drug Delivery Approaches for Herbal Hepatoprotective

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Abstract

The photo-phospholipid complexation technique has emerged as one of the most leading methods of improving bioavailability of phytopharmaceuticals having poor competency of solubilizing and crossing the biological membranes. Complexes between a pure phospholipid and a pure active substance are called phytosomes. Several plant actives in spite of having potent *in vitro* pharmacological activities have failed to demonstrate similar *in vivo* response. One of the newest and most popular lipid-based nano-carriers for delivering herbal-based drug is the nano-phytosome. Despite being created for medicinal uses, nano-phytosome technology has the potential to be used to food items to create unique functional meals. Compared to typical herbal extracts in dosage form, phytosomes exhibit superior absorption due to their water-soluble herbal extract and lipophilic outer layer, which results in better bioavailability and effects. Different methods have been adopted to formulate phospholipid complexes of plant extractives utilizing varying solvent systems, molar ratios of drug/phospholipids and different drying techniques. Some methods of formulating such drug-phospholipid complexes have been patented as well. However, the stability of phyto-phospholipid complexes is still a matter of concern which needs attention. But still a number of products exploiting this technique are under clinical trials and some of them are now in market. The current review highlights key finding of recent years with our own viewpoints which can give the new directions to this strategy as well as study also includes advancements in the technical aspects of phyto-phospholipid formulations which have been done in recent past with future challenges.

Keywords: Phospholipid complex • Phyto-phospholipid • Hepatoprotective potential • Cellular structure

Introduction

The liver: Hepatocytes make up the vital organ known as the liver, which is crucial in controlling several physiological functions like metabolism, secretion, and storage. It can efficiently synthesis helpful principles and eliminate harmful chemicals. Additionally, it assisted in biotransformation and the body's excretion of xenobiotics like pharmaceuticals. Highly reactive oxygen species (ROS) such peroxides, epoxides, and other reactive radicals are produced during the detoxification and excretion of xenobiotics (Phase I and II processes). In order to maintain the equilibrium, the liver produces endogenous antioxidant substances and enzymes (such as SOD, catalase, and vitamin E) as well as GSH, ascorbic acid, and ascorbic acid. Hepatic illness and damage are brought on by oxidative stress, which is brought on by excessive ROS formation.

Liver disease: The most prevalent liver conditions are various forms of acute (sudden) and chronic (long-term) hepatitis (inflammation), fatty liver, cirrhosis (scarring), and cancer. The most frequent causes of these liver illnesses are viruses, medications, and alcohol, as well as metabolic, immunological (defense), and genetic (hereditary) problems. The liver can become inflamed as a result of several common disorders. This inflammation may develop into cirrhosis, or scarring. Patients with cirrhosis, caused by any kind of liver disease, must seek medical attention immediately because they run a higher risk of developing liver cancer or liver failure. A multimodal strategy, involving radiation therapy, medicine, or surgery, including liver transplantation, can be used to treat liver cancer and liver insufficiency. Acute liver failure is the term used to describe the sudden onset of severe acute liver damage in a person who previously had a healthy liver or had well-compensated liver disease, together with reduced synthetic function and encephalopathy. Both acute and chronic liver conditions can impair liver functioning and result in symptoms. The liver has a considerable capacity for reserves. In other words, before a disease affects the liver's capacity and manifests symptoms, the liver often needs to sustain significant damage. Examples of such symptoms are:

Bleeding or easy bruising that can occur when the liver is unable to make enough of the normal blood clotting proteins

- Edema, or fluid-filled swelling of the legs, which can happen when the liver cannot produce enough albumin and the serum albumin level drops too low.
- Unknown-cause fatigue that might be brought on by the liver's poor metabolic process.

Treatment in liver disease: There are few safe and effective synthetic medications for the treatment of hepatic diseases despite the spectacular expansion of contemporary medicine. Both conventional and contemporary drugs are accessible as therapies for liver problems. Anti-inflammatory, immunomodulatory, corticosteroid, antiviral, sadenosyl-L-methionine, -Lipoic acid, dipeptide caspase inhibitor, and ursodeoxycholic acid are among the contemporary treatments (UDCA). For the treatment of liver illnesses, a hydrophilic bile acid with potential immunomodulatory properties and prednisone in conjunction with azathioprine are also chosen. On the other hand, Indian medical systems advocate using a variety of herbs and herbal preparations. These formulas have a long track record of effectiveness and efficiency.

Boerhavia diffusa, Picrorhiza kurroa, Phyllanthus niruri, Phyllanthus emblica, Aloe vera, and others are examples of pharmaceuticals. The blend of flavonolignan from milk thistle, *Silybum marianum*, known as silymarin, has proven to be the most effective natural liver protector. Silymarin is

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Received: 02 January 2023, Manuscript No. jbabm-23-85255; **Editor assigned:** 04 January, 2023, PreQC No. P-85255; **Reviewed:** 17 January 2023, QC No. Q-85255; **Revised:** 23 January 2023, Manuscript No. R-85255; **Published**: 31 January, 2023, DOI: 10.37421/1948-593X.2023.15.367

effective in the treatment of all liver illnesses because it shields liver cells against a wide range of pollutants, radiation, and viral hepatitis. Antioxidant, anti-lipid peroxidant, anti-inflammatory, and ant fibrotic properties are all part of silymarin's mechanism. Silymarin's antifibrogenic qualities have received growing interest; it decreases collagen formation by 30% in secondary biliary fibrosis in rats. Due to its antioxidant activity, it lessens hepatic injury by cytoprotection as well as by preventing the activation of kupffer cells. A clinical trial involving patients with cirrhosis of the liver caused by alcohol consumption found a small survival advantage for treated patients *vs.* untreated controls.

Hepatoprotective potential: The majority of phytosomal research are concentrated on *Silybum marianum*, which has highly effective flavonoids that protect the liver. The milk thistle plant's (*S. marianum, Asteraceae* family) fruit. It has flavonoids with hepatoprotective properties. Silymarin has been demonstrated to be effective in treating a variety of liver conditions, including hepatitis, cirrhosis, fatty liver caused by chemicals and alcohol, and bile duct inflammation. The liver's resilience to toxic assaults is significantly increased by the silymarin's antioxidant capability. Three flavonoids from the subgroup of flavonols make up the majority of silymarin (having a fully saturated C-ring). The three main compounds are *silybin, silydianin*, and *silychristin*. Silybin is a flavonolignan that is likely created by the plant when a flavonol and a coniferyl alcohol are combined. The most powerful of the three, silybin, is now recognised as such. Silybin safeguards the liver by preserving glutathione in the parenchymal cells, and PC aids in cell membrane repair and replacement. These ingredients most likely work in concert to protect liver cells from degeneration. In its natural state, silybin mostly appears complexed with sugars as a flavonyl glycoside or flavonolignan in the milk thistle fruit. Despite having a low bioavailability, silybin has been discovered to exhibit outstanding bioactivity in comprehensive studies. Because of a striking improvement in the lipophilic characteristic of the silybin-phospholipid complex and an improvement in the biological action of silybin, the bioavailability of silybin in the study's rats was significantly raised following oral administration of the complex. According to Tedesco, et al., silymarin phytosomes have more antihepatotoxic action than silymarin alone and can shield broiler chicks from the detrimental effects of aflatoxin B1. Phyto denotes a plant, and some implies something that resembles a cell. The Phytosomes method creates a tiny cell that safeguards the precious herbal extract component from being destroyed by digestive secretions and gut bacteria. The majority of herbal medications' bioactive ingredients are water-soluble compounds. However, water-soluble phytoconstituents, such as many flavonoids, are poorly absorbed (2) either because of their large, multiple-ringed molecules, which prevent simple diffusion from absorbing them, or because of their poor miscibility with oils and other lipids, which severely restricts their ability to cross the lipid-rich outer membranes of the enterocytes in the small intestine. Phytosomes are lipid-compatible molecular aggregates that may be formed from water-soluble phytoconstituent molecules, primarily polyphenoles. Due to their improved ability to pass through lipid-rich biomembranes and eventually enter the circulation, phytosomes are more potent than basic herbal extracts. Phospholipids from soy, primarily phosphatidylcholine, are the lipid-phase materials used to create phytoconstituents that are compatible with lipids (PC). PC, the main molecular component of cell membranes, is miscible in both water and environments rich in lipids and oils and is readily absorbed when taken orally. In contrast to triglycerides, which have three fatty acid bonds, phospholipids only have two fatty acid bonds, with a phosphate group occupying the third site. Numerous well-known herbal extracts have been subjected to the phytosome process, including ginseng, milk thistle (*Silybum marianum*), grape seed, hawthorn, milk thistle extract, and Ginkgo biloba (Panax ginseng). These herbal extracts' flavonoid and terpenoid components are ideally suited for direct binding to phosphatidylcholine. The current paper examines the numerous facets and most recent developments in phytosomal research on diverse plant materials for possible therapeutic applications.

Phytosome: Any herbal medication's efficacy depends on the therapeutically active component being delivered at an appropriate dosage. When given orally or topically, their bioavailability is severely constrained. Recently developed herbal compositions called phytosomes are more absorbable than extracts. Phyto implies a plant, while some meanings like a cell. Numerous botanical items have been shown to have compositions, biological activities, and health advantages throughout the past century thanks to advances in phytochemical and phytopharmacological studies. The majority of a plant's physiologically active components are polar or water-soluble compounds. However, water-soluble plant components, such as flavonoids, tannins, and glycosidic aglycones, are poorly absorbed either because of their large molecular size, which prevents passive absorption, or because of their poor lipid solubility, which severely restricts their ability to cross lipid-rich biological membranes and leads to poor bioavailability. Since ancient times, complex chemical concoctions made from plants, or phytomedicines, have been utilised to maintain health. However, many phytomedicines' efficiency is constrained due to their low oral absorption. By adding phospholipids to standardised extracts, the Italian company Indena S.p. Phytosome A.'s technology significantly increases the bioavailability of some phytomedicines, greatly improving their absorption and use. Chemical and pharmaceutical research has revealed the chemical makeup, biological functions, and health advantages of many plant extracts throughout the past century. However, when parts were removed from the whole, it frequently resulted in a loss of activity and the natural ingredient synergy. As standardised extracts were developed, their therapeutic value was frequently constrained by inadequate bioavailability. The bioavailability of such extracts was then found to be significantly enhanced by complexation with a few additional therapeutically relevant nutrients. The phospholipids are the nutrients that are particularly beneficial for improving the absorption of other nutrients. All known living forms require phospholipids, which are intricate chemicals, to create their cell membranes. They serve as the building blocks of the cell membrane, forming the matrix into which a wide range of proteins, including receptors, transport proteins, enzymes, and other biological energy converters, can fit. The phospholipids are also used in humans and other higher animals as natural digestion aids and as transporters for nutrients that are both fat- and water-soluble Pharmacokinetic (tissue distribution) and activity investigations carried out on both animals and people have shown that phytosomes have a higher bioavailability than the simpler, less complex plant extracts. The phospholipids' known ability to promote health gives phytosomes an extra depth. Herbosomes is another common name for Phytosome Compared to traditional herbal extracts, phytosomes have a superior pharmacokinetic and pharmacodynamic profile. A continuous matrix is provided by the molecular layer, which is made up of PC and other phospholipids, into which the proteins are inserted (Figure 1).

Antioxidant properties: Silipide, a phytosome from the *Silybum marianum* plant, has antioxidant and free radical-scavenging properties that protect the liver from oxidative damage brought on by high doses of CC14 and paracetamol in rats. The suppression of lipid peroxidation by scavenging reactive oxygen species may be the mechanism through which Silipide shields hepatocytes from oxidative damage. Silipide was used for 2 months in the tests on individuals with Hepatitis B and C viruses, and Buzzelli G, et al. [1] found that it significantly decreased liver function markers linked to hepatocyte necrosis or increased cell membrane permeability. After two months of therapy, serum malondialdehyde levels of patients treated with silipide exhibited a striking decrease (36%) indicating that it has anti-lipoperoxidant effect against free radical assault in people.

Properties of phytosomes: A stoichiometric quantity of the phospholipid reacts with the chosen polyphenol (such simple flavonoids) in a nonpolar solvent to form phytosomes. They are solids with a defined melting point that are lipophillic, readily soluble in nonpolar solvents (but not in hydrophilic solvents), and only moderately soluble in fats. They take on a micellar shape when exposed to water, generating structures that resemble liposomes yet vary significantly from them in key ways. While the active ingredient in phospholipid-flavonoid compounds is a component of the membrane, it is dissolved in the medium of the cavity or in the layers of the membrane in liposomes (Figure 1). Specific spectroscopic methods can show that molecules are linked to the polar head of the phospholipids by chemical bonds. In contrast to phytosomes, a liposome is created by combining phosphotidylcholine with a chemical that is water soluble. The molecules of phosphatidylcholine surround the water-soluble material, but no

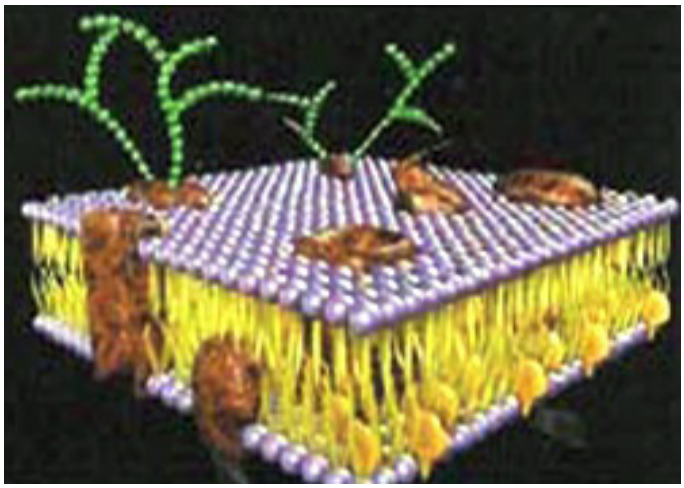

Figure 1. Cell membranes are largely lipid phase.

chemical link is created. The water-soluble substance may be surrounded by hundreds or even thousands of phosphatidylcholine molecules. In contrast, when phosphotidylcholine and the various plant components are processed by phytosomes, they really combine to produce either a 1:1 or a 2:1 complex, depending on the ingredient. Due to this distinction, phytosomes are far more readily absorbed than liposomes.

Mechanism of phytosome technology: A stoichiometric quantity of phosphatidylcholine, a standardised extract, or polyphenolic components (such as simple flavonoids) react in an aprotic solvent to form phytosomes. A bifunctional substance, phosphatidylcholine has a hydrophilic choline moiety and a lipophilic phosphatidylcholine moiety. Phospholipid soluble phosphatidyl part of the phosphatidylcholine molecule, which makes up the body and envelops the choline bound material, specifically binds to these molecules. Thus, the phytomolecules (Figure 2) create a phospholipid and lipid soluble molecular complex known as the phytophospholipid complex. Specific spectroscopy methods can show that molecules are linked to the polar choline head of the phospholipids by chemical bonds. According to a precise chemical investigation, the unit phytosome is often connected to at least one phosphati-dylcholine molecule *via* a flavonoid molecule. Plant extracts' flavonoid and terpenoid components are well-suited for direct binding to phosphatidylcholine. A stoichiometric quantity of the phospholipid (phosphatidylcholine) reacts with a standardised extract or polyphenolic ingredients (such as simple flavonoids) in a non-polar solvent to form phytosomes. A bifunctional substance, phosphatidylcholine has a hydrophilic choline moiety and a lipophilic phosphatidylcholine moiety. There are two basic reasons for the reduced bioavailability and absorption of polyphenolic components. These main components consist primarily of ringed molecules and are not too tiny to be taken in by diffusion.

- The second issue is that the main components of polyphenols, flavonoid molecules, are poorly soluble in lipids.
- These constraints prevent their uptake across cellular membranes. The primary outcome of phytosome technology is the complexation of polyphenols with phospholipid in a 1:1 or 1:2 ratio.

Advantages of phytosome technology: The following advantages provided by the phytosome technology have transformed the nutraceutical sector. One of the phytosome's constituents, phosphatidylcholine, serves as both a transporter and an anti-inflammatory agent with hepatoprotective properties. The phytosome's ingredients are safe and can be used in medicinal products. The bioavailability and absorption of water-soluble phytoconstituents are both improved. Better therapeutic benefits are the outcome of this. The dose needed to elicit desired effects is decreased as a result of enhanced phytoconstituent bioavailability. Comparatively speaking, liposomes are less stable than phytosomes. This is so because chemical bonds are present in the former but not in the latter. The nutritional value of the plant extract is increased by phospholipids. High level of product demand. The creation of phytosomes is a rather easy procedure. The

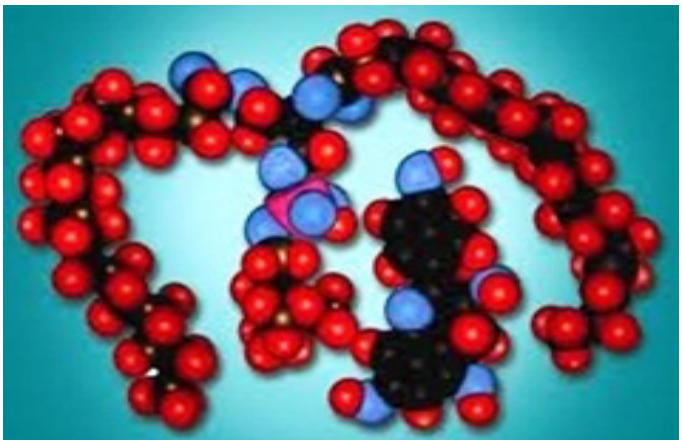

Figure 2. A flavonoid molecule is enveloped by a phospholipids molecule.

ease with which phytosomes can penetrate the skin increases the potency of their effects. Phospholipid protects the water-soluble phytoconstituents from being destroyed by digestive enzymes and gut bacteria. It aids in effective medication delivery to the intended tissue. Phosphatidylcholine, which is a component of cell membrane, not only serves as a transporter but also nourishes skin. Because phytosomes may move from the hydrophilic environment of an enterocyte cell to the lipophilic environment and then within the cell, they can be employed for systematic targeting.

Merits of phytosomes over conventional dosage forms: Due to the complexation of botanical extracts with phospholipids, which boosted component absorption in the digestive system, their bioavailability increased considerably. In contrast to other carriers, phytosme improves the penetration of non-lipophilic botanical extract to enable improved absorption from the intestinal lumen. All of the active ingredients in phytosome have received approval for use in pharmaceutical and cosmetic products, and the formulation is secure. Phytosome is utilized to provide liver-protecting flavonoids due to its high bioavailability. With the use of this technique, phytoconstituents may be delivered at a low cost to various specific sites for pharmacological activity. When utilized as functional cosmetics, phytosomes provide synergistic advantages to protect the skin against exogenous or endogenous risks in both normal and stressed environments. They can be also used for enhancing permeation of drug, through skin in transdermal drug delivery system. They can be widely used in cosmetics due to their improved skin penetration and have a high lipid profile.

An key component of the cell membrane and one of the active ingredients in phytome, phosphatidylcholine serves as a carrier and nourishes the skin. Drug entrapment during formulation development is not a concern. Because the drug itself produces vesicles after conjugating with lipid, the drug's entrapment efficiency with phytsome is high and more than predicted. Because of the chemical linkages that are created between the phosphatidylcholine molecules and the phytoconstituents, they have a superior stability profile. The phytosomal method can be immediately commercialised because it is passive and non-intrusive. Because of the primary constituent's enhanced absorption, the dosage need is decreased. To obtain the appropriate therapeutic effects, they can also be administered in lesser doses. Low risk profile: Because the toxicological profiles of the phytosomal components are extensively described in the scientific literature, this method carries no risk. Highly appealing market profile for goods using unique technologies. Because there is no complex technological investment needed to produce phytosomes, it is simple to formulate (Figure 3).

Phospholipids: Creating the structural framework for novel drug delivery systems

These are complex substances that may be identified as belonging to

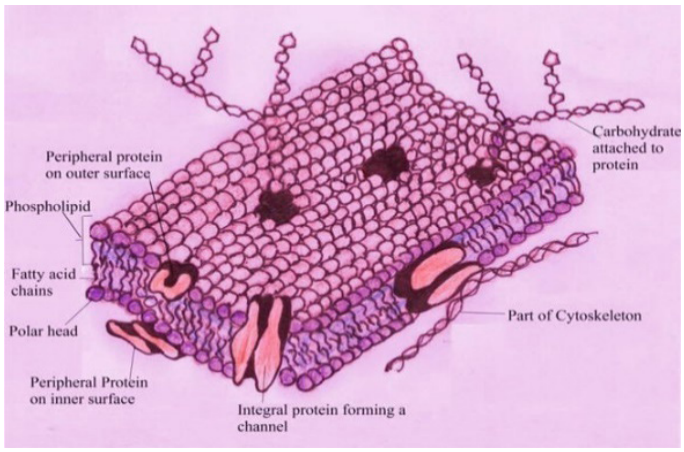

Figure 3. Cell membranes are largely lipid phase. A double molecular layer consisting of PC and other phospholipids provides a continuous matrix into which the proteins.

a certain nutritional category according to their chemical, biochemical, and nutritional features. They are intricate lipid molecules that are crucial for life and are present in every human along with the other recognised components of cell membranes. The tremendous therapeutic effects of phospholipids as dietary supplements mirror their significance in biochemistry. The full range of vitamins, minerals, metabolites, and herbal medicines are easily soluble in the phospholipids. In cell membranes, dietary phospholipids and omega-3 fatty acids act in functional harmony. When taken orally, phosphotidylcholine is a bi-functional molecule that is miscible in both water and oil environments. Phosphatidylcholine is a bioactive nutrient with demonstrated therapeutic benefit for liver illness and is not only a passive "carrier" for the bioactive chemicals (including alcoholic hepatitis). Egg yolk, brain tissue, and a wide range of plant and animal oils all include phosphatidylcholine. It is frequently found in biliary fluid to aid in emulsifying dietary components for absorption (Figure 4).

Bioavailability of phytosomes: Numerous research investigations have shown that phytosomes have better bioavailability and absorption than traditional methods. *Silybum marianum* (milk thistle), whose fruit includes a water-soluble phytoconstituent (flavonoids) known to have a hepatoprotective effect, is the subject of the majority of research investigations. But the absorption of these flavonoids is low. Silybin is the main and most effective component of milk thistle.

The following is a succinct description of some of the research studies: Barzaghi N, et al. [2] found that when single oral dosages of silybin directly coupled to phosphatidylcholine (silybin phytosome) are supplied, their absorption is about seven times more than the absorption from ordinary milk thistle extract with a 70–80% silymarin concentration produced silymarin phytosome and demonstrated its pharmacokinetics in rats as part of a research project. Rats received oral administration of the phytosome. The findings indicated that silybin's bioavailability and biological effects had significantly enhanced. According to several research, ginkgo phytosome produces superior effects to traditional gingko extract when consumed. A bioavailability research on healthy human volunteers revealed that the levels of terpenes and flavonoids (components of GBE) peaked after 3 hours and lasted for a longer duration of 5 hours. One research found that giving ginkgo phytosome to some individuals with intermittent circulation and Reynaud's illness led to a 30–60% better recovery than giving them regular, standardised GBE (Ginkgo biloba extract).

Applications of phytosome technology and commercially available products based on phytosome technology: Milk thistle (*Silybum marianum*). The use of phytosome technology to *Silybum marianum* (milk thistle), which includes flavonoids, a phytoconstituent that protects the liver, has been the subject of several investigations. Milk thistle has demonstrated efficacy in the treatment of a number of disorders, including cirrhosis, hepatitis, fatty liver, etc Strong antioxidant activity in S. marianum increases the liver's tolerance to potentially harmful substances (*Silybin,*

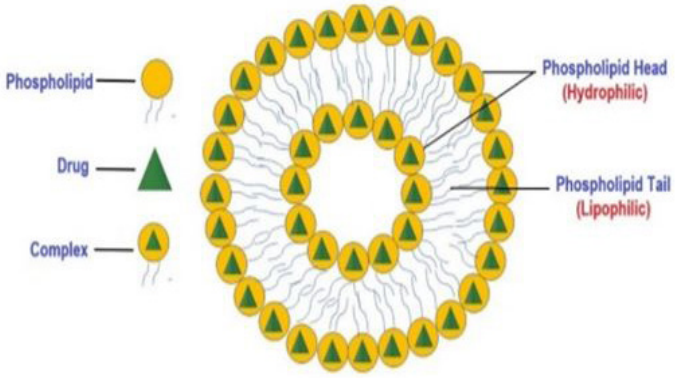

Figure 4 . Structure of photo-phospholipid complexes.

silydianin, and *silychristin* are three of the flavonoids found in S. marianum, with silybin predominating followed by *silydianin* and *silychristin*. The most effective of the three is silybin, which is a flavonolignan Silybin protects liver cells by preserving glutathione in parenchymal cells whilst PC aids in cell membrane repair and replacement. It is evident that silybin has a stronger hepatoprotective impact than other compounds, however this effect is constrained by silybin's low bioavailability, which may be solved by creating a Silybin phytosome. Hesperetin. Hesperetin was combined and complexed with hydrogenated phosphatidyl choline to create a new hesperetin Additionally, its antioxidant activity and pharmacokinetic investigations in CC14-impaired rats were investigated by The study's findings revealed that the phytosome had strong antioxidant activity. According to pharmacokinetic studies, phytosomes have a higher bioavailability than the parent molecule at the same dose

Quercetin The quercetin phytosome in question is Meriva® (500mg) 60VC. When taken orally, the components of curcumin (*curcumin, demethoxycurcumin*, and *bisdemethoxycurcumin)* are poorly absorbed; however, phytosome technology may be able to improve this. Each curcuminoid molecule in Meriva® is uniquely complexed with molecules of the essential nutrient phosphatidylcholine for cell membranes (PC). This improves the therapeutic benefits of curcumin, such as its ability to prevent premature molecular breakdown and support the healthy operation of joints and other organs, as well as its quicker and better absorption into cells. Curcumins' strong antioxidant activity aids in safeguarding cell membrane. Curcumin aids in preventing free radical damage to the DNA, genes, and cell membrane. Despite the vulnerability of membranes to oxidative damage, curcumin serves as a defence to keep them safe from lipid peroxidation

Ginkgo (*Ginkgo biloba*) phytosome. Ginkgo biloba's ginkgoflavonoids make up 24% of its composition. It has an anti-aging effect and safeguards vascular and brain linings. According to certain findings, ginkgo phytosome outperformed conventional standardised Ginkgo biloba extract (GBE), which contains 6% terpene lactones and 24% ginkgo flavones glycoside. A research comparing the bioavailability of ginkgo phytosome and GBE was done on 15 healthy human volunteers. Volunteers were split into two groups and given Ginkgoselect and Ginkgoselect phytosomes, respectively. After a week of wash out, the individuals changed formulas. Each human participant had blood drawn at 30, 60, 120, 180, 240, 300, and 400 minutes after intake. Liquid chromatography/atmospheric pressure chemical ionisation mass spectrometry was used to detect terpene lactones.

In terms of the percentage of oedema reduced, the inhibition of myeloperoxidase activity, and the antioxidant and free radical scavenging characteristics, phytosomes demonstrated substantially higher specific activity and a longer lasting impact than the single components. Using Siliphos [R], a silybin-PC phytosome, at a dosage of 200 mg per kg of body weight, Morazzoni P, et al. [3] demonstrated that silybin levels from Siliphos were enhanced 70 hours after oral administration., however the silybin administered alone didn't really get to measurable levels until 25 hours later. The same group of researchers demonstrated in a another investigation that silybin was found in the plasma within minutes after administration of Siliphos

[R], a silybin-PC phytosome, at a dosage of 200 mg per kg body weight, and that its levels peaked an hour later. After six hours, its plasma levels remained high. It was also demonstrated that phytosomal silybin enters the liver quickly, passes through the liver cells, and enters the bile within two hours. At least 6.5 times more silybin from phytosome dosage reaches the bile than from non-complexed silybin (13% *vs.* 2%, over 24 hours). In contrast to silybin taken orally, silipide (a combination of silybin and PC) has stronger pharmacological action in animal models of hepatic damage, according to research by Pifferi G. [4]. It was also claimed that silipide had substantially higher oral bioavailability and precise organ targeting properties than silybin, which is supplied as a component of silymarin. Jiang, et al. investigated how the Epimedium total Flavonoids Phytosomes (EFP) affected the castrate osteoporosis rat model's ability to prevent and cure bone loss. It was discovered that utilising phytosomes increased E2 level, lowered IL-6 serum concentration, and improved bone density. Jiang YN, et al. [5] improved the procedures for creating flavonoids phytosomes from Herba Epimedii (EFP). The liver is the designated target organ for silybin, as has been demonstrated for rats, and it does so in human beings. Nine volunteer patients who had previously had surgical gall bladder removal due to gallstones were used to demonstrate this. They received single oral doses of 120 mg silybin in the form of silymarin or *silybin phytosome* (*Siliphos*), and their silybin levels were tracked. Silybin first emerged in bile and peaked four hours later. The total quantity of phytosomal silybin recovered in the bile after 48 hours constituted 11% of the whole dosage. Three percent of the silybin in silymarin was successfully extracted. These findings imply that phytosomal silybin passes through the liver four times more frequently. A research looked at the function of phytosomes in the management of non-alcoholic fatty liver disease (NAFLD). The major silymarin component that is absorbed when coupled with a phytosome is silybin. This drug decreases lipid peroxidation and hepatic stellate cell activation in rats. Silybin appears to be able to decrease insulin resistance, liver steatosis, and plasma indicators of liver fibrosis in people, according to some uncontrolled studies. Researchers from Milan and Bari Universities published a controlled study on chronic persistent hepatitis in 1992. Only individuals with biopsy-confirmed hepatitis were included in the research. For many people, the medication therapies for this ailment are ineffective, have serious side effects, and have limited effectiveness. These individuals received one of two 240 mg silybin doses at random. For three months, participants took one capsule twice a day of phytosome n (n=31) or a placebo (n=34). Both the blood ALT and AST levels were significantly reduced in the phytosome group, whereas both enzyme markers increased in the placebo group. Even fewer adverse events were recorded from the silybin medication than from the placebo group, and no patient left the experiment as a result of an unfavourable reaction.

Methodology

Preparation of phytosome: Generally in the preparation of Phytosomes, the phytoactive ingredients such as bioflavonoids, flavolignan and polyphenolic components are reacting drop by drop with a natural or synthetic solution of phospholipids like Phosphatidylcholine (PC) with continuous stirring. For this preparation, phospholipids choose from the different category, for example, Phosphatidyl, ethanolamine, phosphatidylcholine, soy lecithin, from cow-like or swine cerebrum or dermis, Phosphatidylserine in which equal functional group might be same or differ and generally derived from palmitic, stearic, oleic and linoleic acid. The prepared Phytosomes will be isolated then by precipitation with non-solvents, for example, aliphatic hydrocarbons or by lyophilization or by spray drying. Generally in the phytosome complexes the ratio (Tables 1-3).

Rotary evaporator technique: Dissolve particular measure of phytoconstituent and phospholipid appropriate aprotic solvent in a rotating round bottom flask followed by stirring for 3 hours at a temperature not surpassing 40°C. A Thin film of the mixture sample was acquired to which n-hexane/CH3) 2CO was included and consistently blended utilizing a magnetic stirrer. The obtained precipitate was collected, set in amber colored glass bottle and stored at room temperature.

Table 1. Commercial phytosome preparations.

S. No	Name of Phytosome	Method of preparation	Indication/ Application
1	Silybin PhytosomeT	Silybin from Silymarin	Food Product, antioxidant for liver and skin
2	Ginkgo PhytosomeTM	24% ginkgoflavonglycosides from Ginkgo biloba	Protects brain and vascular lining ; Anti-skin Ageing agent
3	Panax Ginseng PhytosomeTM	37.5% ginsenosides from roots of Panax ginseng	Food Product
4	Green Tea PhytosomeTM	epigallocatechin 3-O- gallate from Camelia sinensis	Food Product, Systemic
5	Super Milk thistle Extract	Silybin from Silymarin	FoodProduct; antioxidant
6	Centella phytosomes	Terpens	Food product : in heart disease or hypertension

Table 2. List of materials.

S. No	Materials	Source
1	6-Gingerol	Sigma Aldrich Pvt Ltd, Bangalore
2	Cuminaldehyde	Himedia Laboratories Pvt Ltd, Mumbai
3	Soya Lecithin	Himedia Laboratories Pvt Ltd, Mumbai
4	Chitosan	Himedia Laboratories Pvt Ltd, Mumbai
5	Sodium bicarbonate I.P.	Loba Chemie Pvt Ltd, Mumbai
6	Magnessium stearate I.P.	Loba Chemie Pvt Ltd, Mumbai
7	Hydrochloric acid (AR)	Loba Chemie Pvt Ltd, Mumbai

Table 3. List of equipment's.

S. No	Name of equipment	Model/manufacturer
1	Digital Balance	DJ300S, Shinko Sansui, Japan
2	Digital pH meter	Elico-LI120 pH (type 003), India
3	Magnetic stirrer	Whirlmatic Spectra lab, India
4	Water bath	INSIF, Ambala, India
5	UV Visible Spectrophotometer	Shimadzu-1800, Japan
6	FT-IR Spectrometer (FT-IR)	Shimadzu-8400S, Japan
7	HPLC	Shimadzu, LC solution, Japan.

Antisolvent precipitation technique: The specific amount of lawsone and soya lecithin were taken into a 100 ml round bottom flask and refluxed with 20 ml of dichloromethane at a temperature not exceeding 60°C for 2 h. The mixture is concentrated to 5 -10 ml. Hexane (20 ml) was added carefully with continuous stirring to get the precipitate which was filtered and collected and stored in vacuum desiccators overnight. The dried precipitate is crushed in mortar and sieved through #100 meshes. Powdered complex was placed in amber colored glass bottle and stored at room temperature

Solvent evaporation technique: The specific amount of plant extract, polymer and phospholipids were taken into a round bottom flask and reflux with suitable solvent at a temperature range of 50-60°C for 2 hours. The blend was concentrated to 5-10 ml to get the precipitate which can be isolated and collected for drying. The dried precipitated Phytosomes complex can be placed in an amber colored glass bottle and store at room temperature.

Evaluation of phytosomes

Characterization technique visualization: Visualization of phytosomes can be achieved using transmission electron microscopy (TEM) and by scanning electron microscopy (SEM).

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).

Entrapment efficiency: The entrapment efficiency of a drug by phytosomes can be measured by the ultracentrifugation technique 23.

Transition temperature: The transition temperature of the vesicular lipid systems can be determined by differential scanning calorimeter 24.

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

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 25.

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

1H-NMR, 13C-NMR and IR spectroscopy is undertaken tostudy the complexation and molecular interactions between phosphatidylcholine and components. For the quantification of thermal effects such as fusion, loss of solvent and decomposition of the phytosome is performed by Thermal gravimetric analysis [TGA] and differential scanning colorimetry [DSC]. In addition to those stated above the other methods used are Thin Layer Chromatography [TLC], Infra-Red Spectroscopy, NMR spectroscopy, X-Ray Diffraction Analysis, Scanning Electron Microscopy [SEM], Transmission Electron Microscopy [TEM], Percentage drug entrapment and Photon correlation Spectroscopy [PCS].

1H-NMR The NMR spectrum is engaged for reckoning the formation of complex between the active constituents and phosphatidylcholine portion. In nonpolar solvents there is an evident change in 1H-NMR signal commencing from atoms included in the complex formation. The signals from protons are broadened. In phospholipids there is broadening of signals whereas the singlet correlative to the N-(CH3) 3 of choline yields an upfield shift.

13C-NMR The 13C-NMR of phytosomes, when recorded in C6D6 at room temperature all the carbons of phytoconstituents are unobservable. The signals equivalent to the choline and glycerol portion is broadened whereas some are shifted and most of the resonance of the fatty acids chains maintains their initial sharp lines. FTIR The spectroscopic interpretation of the resultant complex can be firmly established by FTIR. It also confirms the stability by comparing the spectrum of the complex with that of the micro-dispersion in water after freeze-drying at varying time interval. In HPTLC different retention factor values from the phytoconstituents are eluted with the preferred solvent system confirms the formation of a new moiety. DSC and XRD The pure drug, which is crystalline in nature, indicates a sharp peak as high melting point in DSC thermogram whereas resultant phytosome shows a broader peak, which indicates the loss of crystallinity and low melting point than that of pure drug. Similarly the diffraction angle

Discussion

A new delivery system known as a phytosome is produced when phospholipids like phosphatidylcholine and polyphenolic polar phytoconstituents are combined. Phytosomes have unique spectroscopic and physicochemical properties. Similar to liposomes, phytosomes show potential as anti-aging ingredients in cosmetics and as a treatment for various non-pathogenic skin conditions. But phytosomes are preferable to liposomes because of their significantly better absorption and stability profile. The phytosome in herbal remedies is an efficient carrier of a wide range of hepatoprotective phytoconstituents, including flavones, xanthones, and terpenes, among others. After screening and choosing potential phytoconstituents from medicinal plants, phytosomes can be produced for a number of therapeutic objectives, such as cardiovascular, anti-inflammatory, and anticancer effects.

Conclusion

Advanced herbal extracts called phytosomes are more readily absorbed than traditional herbal extracts. Thus, the study discusses the advantages, functional qualities, chemical composition, and production process of phytosomes. The phytosome formulation process is straightforward and is easily adaptable to a commercial scale. These are new complexes that have a much increased absorption profile after oral administration due to greater lipid solubility that enables them to pass through biological membranes, increasing their bioavailability and putting more active ingredient in the systemic circulation. Additionally, phytosomes outperform liposomes in terms of stability and absorption. Phytosomes have been utilized therapeutically for hepatoprotective and liver disorders, as reported in the literature. One can prepare a herbal extract after screening and selecting. A new delivery system known as a phytosome is produced when phospholipids like phosphatidylcholine and polyphenolic polar phytoconstituents are combined. Phytosomes have unique spectroscopic and physicochemical properties. Similar to liposomes, phytosomes show potential as anti-aging ingredients in cosmetics and as a treatment for various non-pathogenic skin conditions. But phytosomes are preferable to liposomes because of their significantly better absorption and stability profile. The phytosome in herbal remedies is an efficient carrier of a wide range of hepatoprotective phytoconstituents, including flavones, xanthones, and terpenes, among others. After screening and choosing potential phytoconstituents from medicinal plants, phytosomes can be produced for a range of therapeutic applications, including cardiovascular, anti-inflammatory, and anticancer activitie

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How to cite this article: Sehrawat, Himanshu, Sourabh Kosey and Junaid Tantray. "Phytosomes: Review on Drug Delivery Approaches for Herbal Hepatoprotective." *J Bioanal Biomed* 15 (2023): 367.