The Journal of Phytopharmacology 2023; 12(1):51-58
Online at: www.phytopharmajournal.com

Review Article

ISSN 2320-480X
JPHYTO 2023; 12(1): 51-58
January- February
Received: 12-04-2022
Accepted: 20-01-2023
Published: 28-02-2023

doi: 10.31254/phyto.2023.12108

Pavan M Patel
Department of Veterinary Pharmacology and Toxicology, College of Veterinary Science and Animal Husbandry, Kamdhenu University, Junagadh, Gujarat, India

Chirag M Modi
Department of Veterinary Pharmacology and Toxicology, College of Veterinary Science and Animal Husbandry, Kamdhenu University, Junagadh, Gujarat, India

Harshad B Patel
Department of Veterinary Pharmacology and Toxicology, College of Veterinary Science and Animal Husbandry, Kamdhenu University, Junagadh, Gujarat, India

Urvesh D Patel
Department of Veterinary Pharmacology and Toxicology, College of Veterinary Science and Animal Husbandry, Kamdhenu University, Junagadh, Gujarat, India

Divya M. Ramchandani
Department of Veterinary Pharmacology and Toxicology, College of Veterinary Science and Animal Husbandry, Kamdhenu University, Junagadh, Gujarat, India

Harsh R Patel
Department of Veterinary Pharmacology and Toxicology, College of Veterinary Science and Animal Husbandry, Kamdhenu University, Junagadh, Gujarat, India

Bhulesh V Paida
Department of Veterinary Pharmacology and Toxicology, College of Veterinary Science and Animal Husbandry, Kamdhenu University, Junagadh, Gujarat, India

Correspondence:
Pavan M Patel
Department of Veterinary Pharmacology and Toxicology, College of Veterinary Science and Animal Husbandry, Kamdhenu University, Junagadh, Gujarat, India
Email: pp6133651@gmail.com

Phytosome: An Emerging Technique for Improving Herbal Drug Delivery

Pavan M Patel, Chirag M Modi, Harshad B Patel, Urvesh D Patel, Divya M. Ramchandani, Harsh R Patel, Bhulesh V Paida

ABSTRACT

Because conventional medicine has a number of adverse side effects on the human body after continuous usage, there has been a new tendency to return to "nature" for the treatment of body disorders. Though their oral bioavailability is poor, flavonoids and other phytoactive components have a variety of nutritional, therapeutic, and preservation effects. Phytosomes are a revolutionary formulation method that addresses the issue of polar phytoconstituents' poor bioavailability while also delivering medications to targeted locations. Other advantages include reduced adverse effects, reduced dosage, improved absorption, and increased drug efficacy. To deliver the medicine to a specific site of action, novel drug delivery uses unique drug carriers such as solid-lipid nanoparticles, nano-structured lipid carriers, lipid vesicles, liposomes, phytosomes, and ethosomes. The physicochemical and pharmacological features of phytosomes, as well as their structure, are discussed in this article. The mechanism of phytosome production is also examined, as well as a variety of traditional and novel formulation approaches were also studied. The methods used to characterise and assess phytosomes provide insight into a number of methodologies that can be utilised to screen certain phytosome features. The pharmacological potential of phytosomes is compared to that of conventional and liposomal drug delivery systems. The scientific significance of a list of important phytosomes patented technologies of various commercially available herbal extracts is also examined.

Keywords: Phytsomes, Novel drug delivery system, Bioavailability, Supercritical fluid methods.

INTRODUCTION

Many active compounds present in medicinal plants (such as flavonoids, tannins, and terpenoids) are poorly absorbed when taken orally, limiting their pharmacological action and ultimately therapeutic application [1]. The poor absorption of active phytochemicals is due to two characteristics: 1) polyphenols' multi-ring structures are too large to be absorbed through passive or non-active absorption, 2) active compounds' limited water or lipid solubility prevents them from passing through the gastrointestinal cells' outer membrane [2].

Active chemicals extracted from natural plants have shown to possess strong *in vitro* pharmacological effects, however *in vivo* absorption has been proven to be insufficient. A number of ways have been proposed [3] to address the issue of poor absorption, including the production of emulsions, liposomes, and nanoparticles, as well as chemical structural modification [4]. Phytosomes (also known as 'Phyto-phospholipid complexes,' 'Supra-molecular complexes,' and 'Herbosomes') have emerged as a potential option for enhancing bioavailability of active ingredients among the many drug delivery systems [2]. Phytosome is made up of two words: Phyto-'plant' and Some-'cell-like.' Herbal medications that have been packaged into vesicles and are available in nano form are known as phytosomes. The phytosome develops an envelope-like coating over the drug's active ingredient, preventing digestive fluids and microbes from destroying the herbal extract's main element [5]. Phytosomes are standardised plant extracts, primarily flavonoids. quercetin, kaemferol, quercretin-3, rhamnoglucoside, quercetin-3-rhamnoside, hyperoside, vitexine, diosmine, 3-rhamnoside, (+) catechin, (-) epicatechin, apigenin-7-glucoside, luteolin, luteolinglucoside among others [6].

One example of a revolutionary drug delivery method that could offer regulated and sustained drug release, allowing for improved pharmacological efficacy at lower dose is targeted drug delivery, which delivers the active component directly to the site of action [5]. Phytosomes are created by interacting phospholipids (natural or synthetic) with specific plant elements in the presence of a suitable solvent, and due to their physical and chemical efficiency, these phyto-complexes can be considered a separate entity. Because they improve therapeutic efficacy, efficiency, and targetability of active components, phytosomes have emerged as a viable drug delivery technique. Thus, phytosome technology is responsible for improved *in-vivo* performance of herbal extracts due to its targeted delivery property;

nano size of phytosomes has resolved the obstacle of poor permeability of large hydrophilic phytoconstituents across biological membrane; increased rate of dissolution and absorption, combined with a better pharmacokinetic profile, relates to better therapeutic effect at lower dose; thus, it can be used in pharmaceutical, nutraceutical, and cosmetic industries [7].

Many phytosome products derived from various herbal extracts, such as silybin phytosome from *Silybum marianum*, grape seed phytosome from *Vitis vinifera* (Grape seed), curcumin phytosome from Turmeric, bilobalide phytosome from *Ginkgo biloba*, and ginseng phytosome from *Panax ginseng*, are already commercially available. Any beneficial chemical that has a structural requirement for direct binding with phosphatidylcholine, such as andrographolide phytosome, clarithromycin-phospholipid complex, glycerrhetinic acid-phospholipid complex, and aceclophenac-phospholipid complex, can be converted to phytosome [8].

HISTORY

Several research are being conducted, and the most recent findings reveal that phytosome technology is a novel technique to improve the absorption and bioavailability of plant extracts while lowering the dose level significantly. The phytosome process was developed in 1989 by ezio bombardelli and gian f. patri of Italy's Indena inc., a prominent producer of nutraceutical components. They discovered that silybin phytosome complex exhibited significantly higher absorption rate than normal silybin.

The hepatoprotective activity of silymarin was tested on nine human volunteers by Schandalik [9], who discovered that the phytosomal form of silybin went through the liver four times faster. A comparable study with 232 chronic hepatitis patients was conducted. He also claimed that the bioavailability of silymarin phytosome is higher than that of the uncomplexed form [10]. Scientists conducted a series of research on silymarin phytosomes in ethanol-induced foetal alcohol syndrome and discovered that the phytosomal form had better fetoprotectant action (increased pup birth weight and lower neonate mortality rate) [11].

Maiti and its coworker developed a quercetin phytosome that shows better therapeutic efficacy in rat liver injury caused by carbon tetrachloride, indicating an increase in anti-oxidant and anti-inflammatory activity [12]. Naringenin and curcumin phytosomes were generated in two separate trials, demonstrating antioxidant activity of the phytosomal complex with better therapeutic efficacy [13]. The C_{max} and AUC values in rat plasma were five fold higher after delivery of phytosome curcumin than after dose of curcumin alone [14]. Phytosomal andographolide has greater absorption and hepatoprotective effectiveness than uncomplexed andrographolide at the same dosage level in rats [15]. They came up with simple phytosome preparation methods. It has been noticed recently that phytosome showing better therapeutic value in cancer than the normal plant extract. Leucoselect phytosome significantly increased chemopreventive effects in lung cancer patients by lowering cardiovascular and neoplastic risks [16].

PROPERTIES OF PHYTOSOME

Chemical properties

The reaction of herbal extracts/molecules with phospholipids in a stoichiometric ratio of 1:1 or 2:1 results in the creation of these complexes. The formation of hydrogen bonds between the polar heads of phospholipids (PO_4 & NH_3) and the polar section of the substrate increases the phytosome's stability [17]. The fatty chain provides unchanged signals in both free phospholipid and the complex, demonstrating that long aliphatic chains do not participate in the reaction and simply wrap around the active principle, according to H^1 NMR and C^{13} NMR data. As a result, it creates a lipophilic sheath that protects them from intestinal microorganisms and stomach secretions [18]. Phytosomes are soluble in non-polar liquids and have a medium solubility in lipids ("Phyto-lipid delivery technique"). When they come into contact with a polar solvent (water), they take on a micellar form (liposomial-like structure).

Physical properties

The size of the phytosome vesicle following the formation of the phyto-phospholipid complex ranges from 50 nm to a few hundred nm, according to photon correlation spectroscopy or transmission electron microscopy. The surface features of phytosomes reveal a spherical shape with a rough surface morphology and strong flowability. When it comes to transdermal medicine administration, particle size is critical. Agglomerates developed more easily due to the high lipid content in the formulation, resulting in bigger particles [19].

Pharmacological properties

The biological behaviour of phytosomes, such as enhanced absorption and utilisation, which leads to better bioavailability, has been shown by pharmacokinetic and pharmacodynamic studies in experimental animals and human subjects. The pharmacokinetic profile of dihydro-myricetin phytosomes is improved, with greater bioavailability due to higher C_{max} and AUC values, as well as a lower clearance rate and volume of distribution [20].

STRUCTURE OF PHYTOSOME

The active polar moiety is docked to a phospholipid that functions as an integral part of the membrane, allowing molecules to be stabilised by hydrogen bonding. The micellar structure of phosphotidylcholine, which is used in phytosomes, is comparable to that of the cell membrane [21].

Formulation Components:

Phyto-phospholipid complexes could be formed by reacting phospholipids with active substances originating from plants. The four necessary components for the production of phytosome are: phospholipids, phyto-active substances, solvents, and thus the ratio quantitative relationship involved in the creation of phytosomes [6].

1. Phospholipids

Egg yolk and plant seeds are the most prevalent natural sources of phospholipid. Phospholipids produced in an industrial setting are commercially available. Phospholipids are classed as glycerophospholipids or sphingomyelins based on their backbone structure. The principal phospholipids utilised to produce complexes with a hydrophilic head group and two hydrophobic hydrocarbon chains are phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine, phosphatidic acid, phosphatidylinositol, and phosphatidylglycerol. The most widely used phospholipid in the formation of phospholipid complexes is phosphatidyl choline. One of the advantages of use of phosphatidyl choline is its moderate solubility in aqueous and lipid environments due to its amphipathic

properties. Furthermore, because it is an essential component of cell membranes, phosphatidyl choline has a high biocompatibility and low toxicity. Hepatoprotective qualities of phosphatidyl choline molecules have been demonstrated, as well as clinical results in the treatment of liver illnesses such as hepatitis, fatty liver, and hepatocirrhosis. In the creation of phytosomes, phospholipids are used as a vehicle-creating component [22].

2. Phyto-active constituents

The phyto-active constituents are usually selected based on significant *in vitro* pharmacological effects rather than *in vivo* activities by the researchers. Flavonoids make up the majority of these chemicals. Quercetin, cathechin, and silibinin are water soluble flavonoids present in plant favouring the aqueous phase and are unable to cross biological membranes. Curcumin and rutin are lipophilic flavonoids that will not dissolve in aqueous gastrointestinal fluids. In the aqueous phase, phytosome complexes increase the water solubility of lipophilic flavonoids and the membrane penetrability of hydrophilic flavonoids. Furthermore, flavonoids can be protected from external impacts such as hydrolysis, photolysis, and oxidation by forming complexes [22].

3. Solvents

For the formation of phytosome complexes, several researchers have utilised different solvents as the reaction medium. Aromatic hydrocarbons, halogen derivatives, methylene chloride, ethyl acetate, and cyclic ethers have all been employed in the past to make phyto-phospholipid complexes, but protonic solvents like ethanol have mainly replaced them. Indeed, protonic solvents such as ethanol and methanol have recently been employed to form phospholipid complexes with success. Polyphenols and phospholipids can interact rationally with these solvents [23]. Many different types of solvents have been successfully studied. Ethanol can be a useful and popular solvent because it leaves fewer residues and causes little damage. Some liposomal drug combinations work when the phytosomes interact with a lower dielectric constant solvent, such as water or a buffer solution. The supercritical fluid (SCF) approach is used nowadays to control the size, shape, and morphology of the substance of interest. The supercritical antisolvent technique (SAS), one of the SCF technologies, is gaining traction as a promising method for creating micronic and submicronic particles with controlled size and size distribution. A supercritical fluid (usually CO_2) is utilised as an anti-solvent to reduce the solute's solubility in the solvent [24].

4. Stoichiometric ratio of active constituents and phospholipids

Phyto-phospholipid complexes are produced by reacting a synthetic or natural phospholipid with the active components in a molar ratio of 0.5 to 2.0 in the majority of cases. In contrast, a stoichiometric ratio of 1:1 is regarded to be the most efficient for creating phytosome complexes since it allows for more interaction between the two components due to the same amount of active substrate and phospholipid present, making it more soluble [25]. A 1:1 stoichiometric ratio is not necessarily appropriate for the synthesis of all phospholipid complexes. The ratios having best physical attributes and loading capacity are selected. The stoichiometric ratio of active components and phospholipids should be modified experimentally for various purposes, such as the maximal drug loading, for various types of pharmaceuticals. The ratio can be chosen based on the combination rate of active entity to phospholipid, which indicated a gradual increase in combination rate up to a 1:1 ratio, after that no further increment is visible [20].

5. pH maintenance

To maintain the pH of the preparation consistent, a buffering agent is used. Two often used buffering agents are saline phosphate buffer (pH 6.5) 7 percent (v/v) and ethanol tris buffer (pH 6.5). The use of buffer is to keep the phytosomes hydrated.

PREPARATION OF PHYTOSOME

Mechanism of phytosome formation

Phosphatidylcholine (also known as phosphatidylserine) is a bifunctional chemical. The lipophilic phosphatidyl moiety is found in nature, while the hydrophilic choline (serine) moiety is found in nature. The dual solubility of the phospholipid makes it a good emulsifier. The choline head of the phosphatidylcholine molecule attaches to these substances, while the lipid soluble phosphatidyl portion of the phosphatidyl molecule, which contains the body and tail, surrounds the choline bound material. As a result, the phytoconstituents form a lipid-compatible molecular complex with phospholipids (also known as phytophospholipid complex), as illustrated in the diagram [2].

The mechanism of phytosome production includes the following steps: Step 1: Presence of phospholipids and plant compounds in aprotic media (for example, dioxane and acetone), Step 2: Hydrogen bond formation Step 2: Wrapping the non-polar tail around the polar complex [26].

CONVENTIONAL METHODS

There are mainly three methods available for preparation of phytosome: 1) Solvent evaporation method, 2) Rotary evaporation method, 3) Anti-solvent precipitation method

1. Solvent evaporation method:

The phytosome can be synthesised utilising the solvent evaporation method. With magnetic stirring at 40°C, phosphatidylcholine is dissolved in 100 mL of non-polar solvent, such as chloroform. The active phytoconstituent is dissolved in 20 mL of a non-polar solvent such as methanol before being added to the phosphatidylcholine-chloroform solution. The clear solution is agitated for 2 h before being dried under vacuum at 60 °C, then transfer to vacuum at 40 °C and dry overnight. Following that, the residue is collected, powdered, and sealed. The resulting light-yellow powder is collected as a phytophospholipid complex [20].

2. Anti-solvent preparation (Salting out method)

Anti-solvent precipitation is used to make phytosomes. In an organic solvent, the bioactive molecule and the phospholipid are dissolved. A rotating vacuum evaporator is used to thoroughly extract the organic solvent at a lower temperature and pressure. In the round bottom flask, a thin layer made of a conjugated mix of phospholipid and bioactive material would form. The solvents are entirely removed from the thin layer with hexane, resulting in a precipitate that is filtered, collected, and stored overnight in vacuum desiccators (24 hrs). Crushed dried precipitate is sieved through #100 meshes in a mortar. The powdered material was maintained in an amber-colored glass bottle at room temperature until testing [27].

NOVEL METHODS

Traditional methods have several drawbacks, including multistep processes, difficulty extraction, and time consumption. Supercritical fluid methods can be used to change the size, shape, and morphology of material of interest. Along with other benefits like as high product purity, crystal polymorphism control, the capacity to process thermolabile substances, a single-step process, and eco-friendly technology. Gas anti-solvents technique (GAS), Supercritical anti-solvent technique (SAS), and Solution enhanced dispersion by supercritical fluids (SEDS) techniques use a supercritical fluid (typically CO_2) as an anti-solvent to limit the solute's solubility in the solvent, whereas Rapid expansion of supercritical solutions (RESS) uses it as a solvent [28].

1. Gas anti-solvents technique (GAS):

It is not required that the CO_2 gas use as an antisolvent should be supercritical. It is injected into the solution in a closed chamber, ideally from the bottom, to achieve uniform mixing. As a result of CO_2 gas dissolution, the organic solvent's solubilization power is reduced, resulting in the precipitation of solutes. The particles are washed with additional antisolvent to remove any leftover solvent. Otherwise, during the depressurization stage, the solutes may resolubilize, jeopardising product stability. In comparison to the solvent antisolvent technique, the gas antisolvent technique produces better results when scaled up to industrial levels.

2. Supercritical antisolvent precipitation (SAS):

By lowering the pressure in the SAS, the solvent is eliminated from the gas phase, resulting in submicrometer-sized particles with a narrow size distribution. It is necessary to have CO_2 in the supercritical condition. The CO_2 and solution are both pumped into a closed chamber from the top. Unlike GAS, this strategy has been proven to work on a broad scale [29]

EVALUATION ATTRIBUTES OF PHYTOSOME

Characterization of phytosome can be done based on physical characteristics such as shape, size, distribution, drug entrapment efficiency, drug release, and chemical composition. Visualization, percentage drug entrapment, NMR spectroscopy, differential scanning calorimetry (DSC), x-ray diffraction analysis (XRD), photon correlation spectroscopy (PCS), and fourier transform infrared spectroscopy (FTIR) are used to characterize them [30].

CHARACTERIZATION OF PHYTOSOME (PHYTO-PHOSPHOLIPID COMPLEXES):

1. Visualization

Phytosomes can be visualised using both transmission electron microscopy (TEM) and scanning electron microscopy (SEM). A soybean phytosome's TEM picture exhibited spherical, rough surface vesicles with no signs of particle aggregation. The drug's internal environment and distribution within the phospholipid mesh can be revealed through TEM investigation. The size of phytosomal vesicles can be measured using TEM at a magnification of 1000 [31]. Scanning electron microscopy (SEM) is used to examine the surface of phytosomes, which revealed no crystalline particles or impurities. The phytosomes' spherical shape is confirmed by the spherical bulging on the surface.

The surface morphologies of the samples are characterised using SEM. Dihydromyricetin-DMY is a tiny prism-like crystal with a regular shape and a smooth surface, according to its description. The surface of HSPC (hydrogenated soybean phosphatidylcholine) has been reported rough and unevenly structured. In the DMY-HSPC complex, the crystal structure of DMY is barely identifiable, and the particle size was smaller than that of DMY and HSPC. However, in the DMY-HSPC physical mixture, HSPC is shown to be only adhered to DMY's crystal surface. These alterations in particle shape indicates that the DMY was dispersed in an amorphous state in the HSPC carrier when the complex formed [20].

2. Vesicle size and zeta potential

Particle size and zeta potential can be measured using dynamic light scattering (DLS) with a computerised inspection system and photon correlation spectroscopy (PCS) [32]. Particle size and zeta potential are two important characteristics of complexes that influence their stability and reproducibility. Phospholipid complexes have particle sizes ranging from 50 nm to 100 m.

A key statistic for nanoparticles is the polydispersity index (PDI), which measures particle size distribution. The particles are termed to be "monodisperse" when the PDI is less than 0.1. In one study of curcumin-phytosomes, phytosome particles were found to be quite homogenous with a PDI of 0.191 and an average size of 131.8 nm.

The particle system is highly stable and capable of preventing particle aggregation if the absolute zeta potential of the particles is greater than 30 mV. If the zeta potential values are in the 20-30 mV range, the particle system is relatively stable. The zeta potential value is a metric for determining a particle system's stability. In the same study above discussed, curcumin-phytosome has a zeta potential of -44.5 mV which makes it a relatively stable system [33].

3. Entrapment efficiency

The ultracentrifugation method can be used to measure a drug's phytosome entrapment efficiency; it shows how much of the drug is imprisoned within the phospholipid mesh. All phytosomes formulations contain about 100 percent of the medicine. The findings show that rutin and phosphatidylcholine bind uniformly [8].

4. Drug content

To determine the amount of drug, a modified high performance liquid chromatographic methodology or a suitable spectroscopic method can be utilised [34].

5. Partition coefficient determination

The partition coefficient may be considered an important feature in TDDS for anticipating skin permeability from an aqueous environment to the lipophilic stratum corneum. For transdermal absorption, the permeant should have a (octanol water) partition coefficient of -1.0 to 4.0. The best phytosome partition coefficient value, with a value of roughly 3, indicating easy penetration from the aqueous environment [8].

The shake-flask method is used to calculate the apparent partition coefficients. Equal volumes of water and n-octanol containing pure drug and phospholipid complex are mixed and equilibrated under steady shaking at 37°C for 24 hours in separate volumetric flasks The two phases are mutually saturated before applying this method [35].

SPECTROSCOPIC TECHNIQUES

Spectroscopic techniques such as nuclear magnetic resonance (NMR), fourier transform infrared spectroscopy (FTIR), and x-ray diffraction study (XRD) are used to confirm the formation of a complex or to study the reciprocal interaction between the phytoconstituent and the phospholipids by comparing the results of the individual component with the complexes [17].

1. NMR technique

Complex structures can be determined using the H^1 NMR and C^{13} NMR techniques. According to NMR data, the formation of hydrogen bonds causes linkage between polyphenols and phospholipids [23]. According to the spectra of different phyto-phospholipid complexes, the hydrophobic side of lipids can cover the core choline-bioactive regions of these complexes.

2. Infrared (IR) spectroscopic analysis

Infrared spectroscopy can also be used to determine the complex's production by comparing the spectrum of the complex to the spectra of the individual components and their mechanical mixing. It also confirms stability by comparing the spectra of the complex to that of the micro-dispersion in water after freeze-drying at various time intervals.

3. X-ray diffraction studies

The loss of crystalline peaks of pharmaceuticals is confirmed when the diffraction angles of phytoconstituents, phospholipids, and phytosomes are compared, revealing the interaction and entrapment of medications inside a sheath that is responsible for increased bioavailability.

4. Differential scanning calorimetry (DSC)

In the DSC thermogram, the crystalline drug moiety shows a strong peak at a high melting point. The melting point of the phytosome is much lower than that of the pure medicine. The large peak suggests crystallinity loss. When phytoconstituents are complexed, their crystallinity is lost, which is responsible for improving the hydrophilicity of hydrophobic phytoconstituents and balancing their hydrophilicity and lipophilicity.

ADVANTAGES OF USE OF PHYTOSOME

The pharmaceutical scope of phytosome are described into following points [36]

- It enhances the absorption of lipid insoluble polar phytoconstituents through oral as well as topical route showing better bioavailability, so it has wide therapeutic benefits**.**
- Phytosomes increases duration of action along with appreciable drug entrapment.
- Phytosomes help to improve the absorption of active constituents and reduces the dose requirements.
- Phosphatidylcholine used in preparation of phytosomes, besides acting as a carrier also acts as a hepatoprotective agent. Hence produce the synergistic effect to the liver targeted drug.
- Chemical bonds are formed between phosphatidylcholine molecule and phytoconstituent, these results in better stability of phytosome.
- Application of phytoconstituents in form of phytosome improves their percutaneous absorption and act as basic carrier for transdermal drug delivery.
- Phytosomal complexes are stable in gastric secretion and resistant to gut bacteria action.
- Phytosome technology has low risk profile since the toxicological profiles of the phytosomal components are well documented in the scientific literature. This is a cost-effective drug delivery because of highly attractive market profile for products with proprietary technology. It is easy to formulate because no complicated technical investment required for the production of phytosomes.

APPLICATION OF PHYTOSOME

Nervous system

Studies have proved the improved efficacy of phytosome on nervous system over the conventional standardized extract. In one study, *Ginkgo biloba* phytosomes generated a significant increase in spontaneous locomotor motor activity indicating higher excitability/stimulation of the central nervous system after treatment with phytosomes. Prolongation of the transfer latency (time to enter the dark chamber) in a dose-dependent way after administration of *Ginkgo biloba* phytosomes in a scopolamine-induced amnesia test in mice clearly indicates its memory-enhancing characteristics and supports their therapeutic usage in alzheimer's illness, Since the scopolamine-amnesia test has been widely acknowledged as a primary screening test for anti-alzheimer drugs [36].

Cardiovascular system

Many studies on grape seed phytosome reported an increase in total antioxidant capacity and stimulation of physiological defenses of plasma, protection against ischemia/reperfusion induced damages in the heart, protective effects against atherosclerosis thereby offering marked protection against the cardiovascular system. In another study, significantly less aortic plaque in the aortas and carotid arteries of rabbit following the grape seed phytosome treatment group than did the control group which received conventional standardized grape seed extract in similar regimen [37]. Studies have proved the improved efficacy of ginkgo phytosome over the conventional standardized extract in protecting rat isolated hearts against ischemia.

Inflammation

Many studies reported better anti-inflammatory activity of phytosome over the pure herbal extract. A study was conducted on the skin uptake of rutin phytosome and found that the rutin phytosomes are better able to penetrate the highly impermeable stratum corneum than free rutin. Retention of this higher quantity of rutin will be available for slow passage through the viable dermis and prolonged anti-inflammatory effect [8]. In a carrageenan induced inflammatory study in rats, inflammation was significantly inhibited by test group rutin phytosome compared to standard diclofenac gel. Because rutin-phytosomes are lipophilic, they have been found to be deposited in the epidermal-dermal region, where the medicine is slowly released to

offer a long-lasting anti-inflammatory effect [38]. A pthalic anhydride (PA)-induced inflammatory study in mice, inflammatory symptoms like erythema, oedema, and erosion on ear and back of mice were drastically reversed after *Centella asiatica* phytosome therapy compared to control and PA treatment group [39]. In another study, the lawsone phytosome gel therapy exhibited significant anti-inflammatory action when compared to plant lawson gel at 4 hours in carrageenan-induced rat paw oedema [40].

Oxidative stress

Studies have shown that phytosomes are having improved anti-hepatotoxic activity compared to standardized herbal extract from plant. In one study on silymarin phytosomes showed higher specific activity and a longer lasting action than pure silymarin with respect to the reduction of oedema, inhibition of myeloperoxidase activity, antioxidant and free radical scavenging activity [41]. In another study, CCL_4 was used to induce hepatotoxicity via degradation of parenchymal cells and damage to adipose tissue when compared to the control group. The anti-oxidant capabilities of apigenin phospholipid complex therapy have a strong hepatoprotective effect by reversing these damages. They also discovered pharmacokinetic parameters like C_{max}, T_{max}, and AUC increased while clearance rate and volume of distribution dropped, indicating improved bioavailability of apigenin nanoparticles (APLC). This is due to two main factors: 1) Higher aqueous phase solubility leads to increased intestinal absorption (because of phospholipid based molecular aggregates) 2) Phospholipids protect apigenin from hepatic first-pass metabolism [42].

Diabetes

In a streptozotocin-nicotinamide induced diabetis study in rats, phytosomes formulation of plant *Momordica dioica* at a lower dose showed more significant blood glucose lowering effect than the conventional total methanolic extract group, which is comparable to the standard metformin group, an anti-diabetic drug [43].

Cancer

Many researchers reported enhanced anti-tumour effect of phytosome formulation compared to normal plant extract. A study of targeting phytosome tumour therapy reported that phytosomes with a molecular weight more than 40 kDa and a nanometric size range of 100–1200 nm actively targets tumour cells because of their improved penetration and retention impact. Active targeting specifically delivers the pharmaceuticals in the site of action, while passive targeting boosts the bioavailability of the drugs. The two are combined in phytosomes to deliver the bioactive ingredients [27]. In another study, MCF-7 cells were treated to increasing concentrations of phytosomal-curcumin and 5-fluorouracil singly and in combination. They found that phytosomal-curcumin suppresses cell growth/invasion in a dose-dependent manner and induces tumour shrinking considerably when compared to single-treated groups, which was linked to higher levels of E-cadherin and MMP9 [44].

Obesity

A study of soy phytosomal thermogel applied topically on rats was found to have a local anti-obesity effect on rats' abdomen with lowering effect on the serum lipid profile. It can be explained by the fact that nanosized particles of phytosome vesicles have a high skin permeation ability that may let it reach the blood circulation showing the cholesterol-lowering property of orally administered soy proteins [31].

Fungal infection

Phytosomal complexes are reported to have increased anti-fungal activity compared to plain herbal extract from plant. One example of the phytosome complex of lawsone showing better antifungal activity when compared to the plant medicine lawsone, and the plain ketoconazole, demonstrated by the maximum zone of inhibition [40].

CONCLUSION

The lipophilic nature of phytosomes improves the drug's pharmacokinetic profile by enhancing complex chemical absorption. The reciprocal interaction between phytoconstituents and phospholipids was demonstrated using sophisticated spectroscopic studies. Hepatoprotective, anti-inflammatory, antioxidant, and anticancer activities are among the therapeutic benefits of the phytosome formulation. Improved solubility, stability, long-term dosing, chemical and physical degradation resistance, and pharmacological efficiency are among the benefits of phytosome formulations over typical herbal formulations.

Conflict of Interest

None declared.

Financial Support

None declared.

ORCID ID

Pavan Patel: https://orcid.org/0000-0003-0575-3338

Chirag Modi: https://orcid.org/0000-0002-2895-4469

Urvesh Patel: https://orcid.org/0000-0002-0580-5356

Harshad Patel: https://orcid.org/0000-0001-8170-5579

Harsh Patel: https://orcid.org/0000-0003-2928-4070

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HOW TO CITE THIS ARTICLE

Patel PM, Modi CM, Patel HB, Patel UD**,** Ramchandani DM, Patel HR, Paida BV**.** Phytosome: An Emerging Technique for Improving Herbal Drug Delivery. J Phytopharmacol 2023; 12(1):51-58. doi: 10.31254/phyto.2023.12108