PHYTOSOMES: A NOVEL HERBAL DRUG DELIVERY FOR THE ENHANCEMENT OF BIOAVAILABILITY AND THERAPEUTIC EFFICACY OF PHYTOPHARMACEUTICALS

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Abstract-

The use of herbal medicines to treat various disorders is widespread around the world. People are drawn to therapeutic herbs because of their minimal side effects. Herbal medicines' uses are limited by the traditional dose form's low absorption, decreased bioavailability, and reduced penetration through biological membranes. To address all of these problems with herbal extract or plant actives, a revolutionary drug delivery system known as Phyto-Phospholipid Complexes (Phyto some) approach was introduced. Using this cutting-edge technology technique, the desired therapeutic effect was produced at a lower dose. Increased pharmacokinetic characteristics, skin penetration through strategic targeting to transition from hydrophilic to lipophilic environments, and improved stability due to chemical coupling. The most recent research on the potential use of Phyto complexes for the treatment of various diseases, their marketable form, the mechanism of Phyto transportation, and the prospects for the future are summarized in this review. The Prospectus of the Phytosomes Method can provide new directions and a boundless frontier as revolutionary medicinal therapy.

Keywords- Phytosomes, Herbal Extract, Delivery System, Herbal medicines, Bioavailability

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1. INTRODUCTION-

The use of herbal medicine dates to early civilizations. It entails the use of plants as medicines to cure illness and improve people's overall health and well-being. In many different national healthcare systems around the world, the usage of herbal medicines is still growing quickly as more individuals turn to these products to treat a variety of health issues. **(1)** Numerous plant

extracts have been the subject of chemical and pharmacological studies throughout the past century to understand their chemical composition and confirm traditional medicine's indications. Most herbal medications' bioactive ingredients are polar or water-soluble compounds. However, many flavonoids, which are phytoconstituents that are water soluble, are poorly absorbed. Due to their massive, multiple-ringed molecules' inability to be absorbed through simple diffusion or their poor miscibility with oils and other lipids, which significantly restricts their capacity to move through the lipid-rich outer membranes of the small intestine's enterocytes resulting in poor bioavailability. **(2)** It has frequently been noted that the natural ingredient synergy is lost when the constituents of an extract are isolated and purified, which may result in a partial or complete loss of particular bio-activity for the purified constituent. The chemical complexity of the raw or partially purified extract frequently appears to be important for the bioavailability of the active ingredients. When extracts are consumed orally, some of their contents may be degraded in the gastric environment. Despite the development of standardized extracts, low bioavailability often, these factors limit their clinical value. **(3)** The bioavailability of such extracts was then found to be significantly increased by complexation with a few other clinically relevant nutrients. The phospholipids are the nutrients that are particularly beneficial for improving the absorption of other nutrients.

The creation of novel drug delivery systems (NDDS) for herbal medicines has received a lot of interest during the last few decades. Idealistically, the novel carriers should meet two requirements. The medicine should first be delivered over the course of treatment at a rate determined by the body's needs. Second, it should direct the herbal drug's active ingredient to the site of action. None of these can be satisfied by conventional dosage forms, including prolonged-release dosage forms. A variety of novel formulations like polymeric nanoparticles, nanocapsules, liposomes, pyrosomes, ribosomes, nanoemulsions, microspheres, transferases, and ethosomes have been reported using bioactive and plant extracts. The novel formulations are reported to have remarkable advantages over conventional formulations of plant actives and extracts which include enhancement of solubility, bioavailability, protection from toxicity,

enhancement of pharmacological activity, enhancement of stability, improved tissue macrophages distribution, sustained delivery, and protection from physical and chemical degradation. **(4)**

Phyto-phospholipid complex (phytosome) is a novel approach to drug delivery systems. Phytosomes is a patented technology developed by Indena S.p.A. of Italy, whereby the individual component of standardized plant extracts are bound to phosphatidylcholine - an emulsifying component to produce lipid-compatible molecular complexes, called Phytosomes and so vastly improve their absorption and bioavailability. They are better able to penetrate lipid-rich biomembranes and eventually reach the blood. **(5)** Phospholipids from soy, particularly phosphatidylcholine (PC), are used as lipid-phase components to create phytoconstituents that are compatible with lipids. **(6)** All known life forms require phospholipids, which are intricate chemicals, to create their cell membranes. "Phyto" is short for plant, while "some" is short for cell-like. It is also called ribosomes. The Phytosomes mechanism creates a small cell, which protects the herbal extract's valuable components from being destroyed by digestive secretions and intestinal bacteria. Phytosomes are better at transitioning from a hydrophilic state to the lipid-friendly environment of the enterocyte cell membrane, than into the cell and eventually into the bloodstream.**(7,8)**) Therefore, the most beneficial use of pyrosomes is the absorption of drugs in the form of reversible complexes with phospholipids, which demonstrated that these complexes have more potent and long-lasting anti-inflammatory and Vaso kinetic effects than those seen after administering the same amount of the substance in free form. **(9)** A potential method for the delivery of herbal medicines and nutraceuticals is phytosomes. Numerous well-known herbal extracts, such as ginseng, ginkgo biloba, grape seed, hawthorn, milk thistle, and green tea, have been subjected to the phytosomes procedure.**(10)**

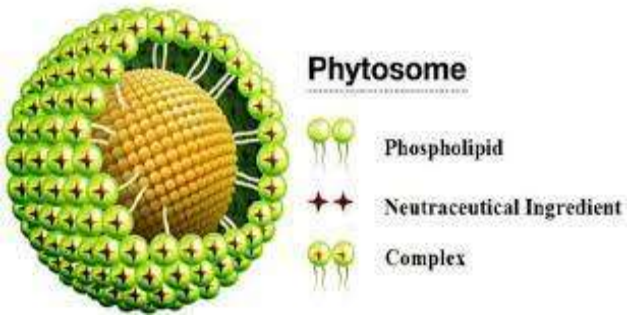

Fig. 1- Basic structure of Phytosome

1. Method of Preparation of Phytosomes –

Different processes are used to combine one mole of phytoconstituents with 3-2 moles of natural or synthesized phospholipids, primarily phosphatidylcholine. The range from 0.5 to 2.0 moles is the most ideal ratio for the development of complexes between these two moieties. [(11-12)] The table below describes numerous phytosome preparation techniques.

Table 1- Methods used for the preparation of Phytosomes

Methods	Procedure
Solvent evaporation method	A 100 mL circular bottom flask is filled with the necessary amount of plant material and phospholipids, along with 20 mL of acetone, and is then refluxed for two hours at 50–60°C. The precipitate was filtered off after the mixture was condensed to 5–10 mL. The dried precipitate phytosome complex was stored at room temperature in an amber-colored glass container. [(13)]
Rotary evaporation technique	A rotating circular bottom flask was used to dissolve the appropriate amount of plant material and phospholipid in 30 mL of tetrahydrofuran. The mixture was then stirred for three hours at a temperature below 40°C. N-hexane was added after a thin layer of the sample was collected, and the mixture was continually agitated using a magnetic stirrer. The precipitate was taken out and cooled to room temperature in a glass container that was amber in color. [(14)]
Ether-injection technique	In this process, an organic solvent is used to dissolve the drug lipid complex. After that, vesicles are created by slowly injecting the mixture into an aqueous agent that has been heated. The focus of amphiphiles determines their state. Amphiphiles take on a monomer form while the concentration is low, but as the concentration rises, other configurations, such as circular, cylinder, disc, cubic, or hexagonal structures, may appear. [(15)]

Mechanical Dispersion method	In this procedure, the drug-containing aqueous phase comes into touch with the lipids that have been dissolved in an organic solvent. The phytoconstituents to be encapsulated are initially dissolved in diethyl ether, which is then gently added to an aqueous solution. The synthesis of the Phyto phospholipid complex is caused by the subsequent elimination of the organic solvent under reduced pressure. Supercritical fluids (SCF), which comprise the compressed anti-solvent procedure (PCA), supercritical anti-solvent method (SAS), and gas anti-solvent technique (GAS), are new techniques for producing phospholipid complexes.[16,17]
Lyophilization technique	Lyophilization process Both natural and synthetic phospholipids and phytoconstituents are dissolved in various solvents, and then additional solutions containing the phytoconstituent were added to solutions already containing the phospholipids, which were then stirred until complex formation occurred. By lyophilization, the produced complex is isolated. [18]
Salting out method	Phosphatidylcholine and phytoconstituents are dissolved in an aprotic solvent, such as dioxane or acetone, where the solution is agitated overnight. The generated complex is then separated by precipitation from a non-solvent, such as n-hexane. [19]
Antisolvent precipitation technique	A 100 ml round bottom flask was filled with the exact amount of medication and soy lecithin, and it was refluxed for two hours at a temperature of no more than 60 o C with 20 ml of dichloromethane. To 5–10 ml, the mixture has been concentrated. To obtain the precipitate, hexane (20 ml) was carefully added while stirring continuously. The precipitate was then filtered, gathered, and overnight stored in vacuum desiccators. In a mortar, the dry precipitate is broken up, and then it is sieved through #100 meshes. Complex that had been ground up was put in an amber-colored glass bottle and kept at room temperature. [20]
Super Critical Fluids (SCF)	Three separate traditional procedures were used to create the complex. Comparing the complex created by the supercritical anti-solvent precipitation process favorably to solvent evaporation, lyophilization, and micronized puerarin. Two SCF techniques were used. GAS (Gas anti-solvent technique) and SEDS (Solution enhanced dispersion by supercritical fluids) have been used for the preparation of complexes. The drug and phospholipid solutions were individually mixed with a supercritical antisolvent in the GAS method until the desired final pressure was attained. The reaction vessel was then maintained at a constant 38 °C and 10 mPa pressure for 3 hours without any agitation. In the SEDS method, the supercritical anti-solvent and liquid solution were constantly added to the precipitation unit. A 0.1 mm diameter nozzle was used to introduce carbon dioxide gas into a solvent-containing combination of phospholipids and purarin. With a temperature of 35 °C, a pressure of 10 MPa, a drug-to-phospholipid mass ratio of 1%, and a purarin concentration of 100 mg/ml, the experimental conditions were optimized. The final procedure generated a 93% yield complex. [16,21]

2.1. Various properties of Phytosomes:

Chemical properties: A natural substance and organic phospholipids, such as soy phospholipids, come together to form phytosomes. By reacting stoichiometric concentrations of the substrate and phospholipid in the right solvent, one can create this complex. Spectroscopic studies have demonstrated that the primary phospholipid-substrate interaction results from the creation of hydrogen bonds between the polar functionalities of the substrate and the phosphate and ammonium groups of phospholipids. When exposed to water, phytosomes take on a micellar shape and produce structures resembling liposomes. In liposomes the active principle is dissolved in the internal pocket or it is floating in the layered membrane, while in phytosomes the active principle is anchored to the polar head of phospholipids, becoming an integral part of the membrane for example in the case of the catechindistearoyl phosphatidylcholine complex, in this there is the formation of H-bonds between the phenolic hydroxyls of the flavone moiety and the phosphate ion on the phosphatidylcholine side. **(22)**

Phosphatidylcholine: This can be inferred by contrasting the complex's NMR with that of its pure predecessors. The fatty chain's signals essentially remain unaltered. These findings suggested that the two long aliphatic chains wrap around the active ingredient to create a lipophilic envelope that protects the catechin and the polar head of the phospholipid. **(23)**

Biological properties: Modern herbal compounds called phytosomes are better absorbed, used, and thus offer better effects than traditional herbal extracts. It has been shown that the phytosome has a higher bioavailability than the less complex botanical derivatives. by conducting pharmacodynamic and pharmacokinetic testing on humans, animals, and other test subjects. **(24)**

1. **Characterization and evaluation of phytosomes-**

The behavior of phytosomes in both physical and biological systems is governed by the factors such as physical size membrane permeability; percent entrapped solutes, chemical composition as well as the quantity and purity of the starting materials. Therefore, the phytosomes are characterized by physical attributes i.e., shape, size,

distribution, percentage drug capture entrapped volume, percentage drug released, and chemical composition. Methods used for their characterization are Infra-Red Spectroscopy, NMR Spectroscopy, Differential Scan Calorimetry, Transmission Electron Microscopy (TEM), Photon correlation Spectroscopy (PCS), (NMR) Nuclear Magnetic Resonance, Percentage drug entrapment, Solubility study, etc. [25]

3.1 Characterization Techniques:

3.1.1.Visualization: Visualization of phytosomes can be achieved using transmission electron microscopy (TEM) and scanning electron microscopy (SEM). With a 1000x magnification, TEM is used to characterize the size of phytosomal vesicles, and SEM is utilized to assess the particle's size and appearance. The dry sample is applied to a gold-coated brass stub of the electron microscope. [26]

3.1.2. Particle size and zeta potential: By employing a computerized inspection system and photon correlation spectroscopy (PCS), dynamic light scattering (DLS) can be used to determine the particle size and zeta potential. [27]

3.1.3. Transition temperature: To determine the vesicular lipid system's transition temperature, differential scanning calorimetry is performed. The drug-phospholipid complex, drug polyphenolic extract, phosphatidylcholine, a physical mixture of the drug extract and phosphatidylcholine, and the drug were all added to an aluminum cell and heated at a rate of 50–250 °C/min from 0 to 400 °C in a nitrogen atmosphere. [28]

3.1.4. Surface tension measurement: The ring method in a Du Nouy ring tensiometer can be used to assess the drug's surface tension activity in an aqueous solution. [29]

3.1.5. Entrapment efficiency: The ultracentrifugation method can be used to determine how well a medication is captured by phytosomes. The drug phytosomal complex was centrifuged at 10000 rpm for 90 minutes at 4°C to separate phytosome from the untrapped drug. The concentration of the free drug can be measured by doing ultraviolet spectroscopy. [30]

3.1.6. Vesicle stability: The stability of vesicles can be estimated by monitoring the size and structure of vesicles over time. DLS measures mean size, while TEM tracks structural changes. [31]

3.1.7. Drug content: A customized high-performance liquid chromatographic method or an appropriate spectroscopic method can be used to quantify the amount of medication. **(32)**

3.2. Evaluation of Phytosomes:

The following spectroscopic techniques are employed to confirm the development of a complex or to investigate the reciprocal interaction between the phytoconstituent and the phospholipids.

3.2.1. Proton-Nuclear Magnetic Resonance (¹H-NMR): Bombardelli et al. examined the (+) catechin's NMR spectra as well as that of its stoichiometric combination with distearoylphosphatidylcholine. The 1H-NMR signal coming from the atoms involved in the complex's creation undergoes a noticeable change in nonpolar solvents, but there is no summation of the signal specific to each individual molecule. In order to prevent the proton from being released, the signals from the flavonoids' protons must be strengthened. When it comes to phospholipids, all of the signals expand while the singlet corresponding to the choline's N(CH3)3 undergoes an upward shift. The sample is heated to 60 °C, which causes the emergence of certain new broad bands that primarily correspond to the resonance of the flavonoid moiety. **(33)**

3.2.2. Carbon-Nuclear Magnetic Resonance (¹³C-NMR): All of the flavonoid carbons are visibly absent in the spectrum of (+)-catechin and its stoichiometric combination with distearoylphosphatidylcholine, especially when recorded in C6D6 at ambient temperature. While most resonances of the fatty acid chains maintain their original sharp line shape, signals related to the glycerol and choline portion of the lipid (between 60 and 80 ppm) are broadened and others are displaced. All of the flavonoid moieties' signals reappeared after heating to 60, however, they were still very broad and somewhat overlapped.

3.2.3. Fourier-Transformed Infra-Red (FT-IR) Spectroscopy (FTRI): By contrasting the spectrum of the complex with the spectra of the individual components and their mechanical mixes, IR spectroscopy can also be used to confirm the complex's creation. When microdispersed in water or included in very basic cosmetic gels, FTIR spectroscopy is also a helpful method for controlling the stability of

phytosomes Furthermore, the stability may be verified by contrasting the complex's spectra in solid form (phytosomes) with that of its microdispersion in water following lyophilization, at various times. For simple formulations, it is required to subtract the cosmetic form's spectrum at various points and then contrast the resulting spectrum of the complex as a whole. **(34)**

3.2.4. X-ray diffraction (XRD): The structure of crystalline materials, including atomic arrangement, crystalline size, and flaws, can be studied via XRD analysis. Results utilizing a graphite monochromatic at a count rate of 103.99 C with a Phillips X-Ray diffractometer (Model 1130/90). Currently, X-ray diffraction is a useful technique for analyzing the microstructure of some amorphous materials as well as crystalline ones. On either active ingredients or active constituents of phytophospholipid complexes, PCs, and their physical mixes, X-ray diffraction is generally conducted. **(35)**

3.3. In vitro and In vivo evaluations

Selection of in-vitro and in-vivo evaluation models is based on the anticipated therapeutic efficacy of phytoconstituents obtainable from the phytosome. For instance, the antioxidant and free radical scavenging activity of phytosomes can be used to evaluate in-vitro antihepatotoxic efficacy. To evaluate produced phytosomes' in vivo anti-hepatotoxic activity, and their impact on animals when exposed to thioacetamide, paracetamol, or alcohol-induced liver damage, examining hepatotoxicity is possible. The in-vivo safety evaluation process is described in research on the skin sensitivity and tolerability of a commercial product called glycyrrhetinic acid phytosome ointment. **(10,36)**

3.4. Applications of phytosome technology

When compared to the traditional plant extracts, other phytosome compounds have shown meaningful therapeutic results.

3.4.1. Hepatoprotective Effect of Phytosome.

Phosphatidylcholine is a crude component that, like other carriers used in different drug delivery methods, also has a lot of medicinal advantages. **(37)** It will be demonstrated that phosphatidylcholine's synergistic impact protects the liver. Phospholipids can occasionally have a nutritional purpose.Silybum marianum, also known as milk thistle, is the subject of the majority of phytosome investigations because it contains

powerful liver-protecting flavonoids. Three flavonoids with a fully saturated C ring, or flavonols, make up the majority of silymarin. The three main compounds are silybin, silydianin, and silychristin. Silybin is a flavonolignan that probably formed naturally in the plant when a flavonol and a coniferyl alcohol combined. The strongest of the three is now understood to be silybin. Silymarin has been demonstrated to be effective in treating a variety of liver conditions, including cirrhosis, hepatitis, fatty infiltration of the liver (chemical and alcohol-induced fatty liver), and bile duct inflammation. Silymarin's antioxidant abilities significantly increase the liver's tolerance to harmful substances. The Milk thistle plant produces flavonoids in its fruit that have been shown to have hepatoprotective properties. The main and most effective component of Silymarin, the milk thistle flavonoids complex, is silybin. Although Silybum marinum's standardised extract is a great liver protector, it is not well absorbed when taken orally. [38,39]) According to Busby et al., a Silymarin phytosome demonstrated superior fetoprotectant action against ethanol-induced behavioural impairments to uncomplexed Silymarin. [40] A human investigation was carried out by Barzaghi et al. [41] to evaluate the absorption of Silybin when it was directly linked to PC. After giving healthy participants a single oral dose of Silybin phytosome and a comparable dose of Silybin from milk thistle, the plasma Silybin levels were assessed. According to the findings, silybin from the silybin phytosome is absorbed almost seven times more readily than silybin from the conventional milk thistle extract, which contains between 70 and 80 percent silymarin.

3.4. 2. Cardiovascular properties of phytosomes: Leucoselect PHYTOSOME is a phytosome preparation based on grape anthocyanidins. Grape seed phytosome is composed of polyphenols complexed with phospholipids. It has a strong antioxidant activity and is cardioprotective. [42] The effectiveness of ginkgo-selected phytosomes was shown to be 30–60% higher than that of ginkgo selected in the treatment of peripheral vascular illness (such as Raynaud's disease and intermittent claudication). Additionally, recently confirmed as a cardioprotective agent is ginkgo-select phytosome. [43]

3.4. 3. Anti-aging properties of Phytosome: The utilization of phytosomes as a delivery mechanism in the cosmetic industry presents the novel potential for the use of active substances. Investigations into the Ginkgo Biloba PHYTOSOME for the treatment of sagingeing linked to superficial capillary blood flow have been conducted. Oral G. biloba extracts are used to increase peripheral circulation, and topical G. biloba phospholipid complexes have been shown to increase skin microcirculation. The use of Silymarin PHYTOSOME® in treating aging skin has also been documented, along with a study of PHYTOSOME®'s function in functional cosmetics.**(44,45,46)**

3.4.4. Improve bioavailability and anti-oxidant properties: A fully standardised polyphenol fraction (not less than 66.5%) obtained from green tea leaves and present in Greenselect phytosome is primarily characterised by the presence of epigallocatechin and its derivatives. These substances are potent homeostasis-breaking biochemical process modulators in major chronic degenerative disorders like cancer and atherosclerosis. Mirtoselect phytosome was created by complexing anthocyanosides extracted from bilberry (Vaccinium myritillus) extracts. It strengthens capillaries, lowers aberrant blood vessel permeability, and has strong antioxidant properties. According to numerous research, phyto-phospholipid complexes can enhance oral topical absorption, hence raising bioavailability and lowering the required dose. Therefore, it has the potential to greatly increase therapeutic advantages. Hesperetin was combined and complexed with hydrogenated phosphatidyl choline to create a new hesperetin. Additionally, its antioxidant activity and pharmacokinetic studies in CC14-impaired rats were investigated by Mukherjee et al. 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 dosage. (47,48) A commercially available phytosome-OleaselectTM PHYTOSOME is available in the market based on olive oil polyphenols. It is a strong antioxidant, anti-inflammatory and antihyperlipidemic. It inhibits the oxidation of LDL cholesterol and is cardioprotective. **(30,49)**

1.5.Commercial phytosomes products:

The phytosome has a better bioavailability than non-complexed botanical versions,

according to pharmacokinetic and pharmacodynamic studies in lab animals and human volunteers. Associated issues have been researched using various commercially accessible goods. The table below describes the formulation of phytosomes that is accessible commercially and has a variety of medicinal uses.

Table 2- Commercially available Phytosomes of various therapeutic applications [50-58]

Commercial product	Biological Source	Indication
Silybin Phytosome[tm] (Siliphos®)	Silybium Maranium	Hepatoprotective, Hepatitis, Cirrhosis And Inflammation, Antioxidant For Liver And Skin, Food Product
Naringenin Phytosome[tm]	Citrus Aurantium	Antioxidant Activity
Ginkgoselect Phytosome®	*Ginkgo Biloba* L.	Antioxidant Activity, Cognitive Health Support, Healthy Brain Function, Vascular Health
Ginkgo Biloba Phytosome[tm]	*Ginkgo Biloba* L.	Cardio-Protective, Antioxidant Activity
Leucoselect Phytosome®	Vitis Vinifera L.	Antioxidant, Uv Protectant
Green Tea Phytosome[tm]	Camellia Sinensis	Nutraceutical, Anticancer, Antioxidant, Atherosclerosis, Hepatoprotective, Antidiabetic, Anti-Inflammatory, Food Product
Virtiva®	Ginkgo Biloba L.	Cognition Increaser.
Curcumin Phytosome[tm], Curcuvet®(Meriva®)	Curcuma Longa	Osteoarthritis, Anticancer, Anti-Inflammatory
Sericoside	Terminalia Serica	Anti-Wrinkle
Echniacea Phytosome[tm]	Echniacea Angustifolia	Nutraceutical, Immunomodulatory
ESCIN ß SITOSTEROL, PHYTOSOME[TM]	Aesculus Hippocastanum	Anti-Oedema And Vasoactive Properties
Esculoside Phytosome[tm]	Fraxinus Ornus	Vasoactive, Anticellulite
Visnadex[tm]	Ammi Visnaga	Improve Microcirculation
Centella Triterpenoid Phytosome[tm]	Centella Asiatica	Skin Disorders, Antiulcer, Wound Healing, Anti-Hair Loss Agent
Naringenin Phytosome[tm]	Citrus Aurantium	Antioxidant
Hawthron Phytosome[tm]	Crategus Oxyacanthoides	Nutraceutical, Cardioprotective And Antihypertensive
Cucurbita Phytosome[tm]	Cucurbita Pepo	Anti-Inflammatory, Benign Prostatic Hyperplasia
Esculoside Phytosome[tm]	Fraxinus Ornus	Vasoactive, Anticellulite
Pycnogenol Phytosome[tm]	Pinus Maritime	Anti-Inflammatory, Antiwrinkle,

		Antiallergic
Millet Phytosometm	Panicum Miliaceum	Antistress, Beauty Food For Skin, Nails And Hairs
Zanthalene Phytosome[tm]	Zanthoxylum Bungeanum	Soothing And Anti-Reddening
Swertia Phytosome[tm]	Swertia Alternifolia	Antidiabetic
Ximilene And Ximenoil Phytosome[tm]	Santalum Album	Improve Microcirculation
Madeglucyl Phytosome[tm]	Syzygium Cumini	Antihyperglycemic, Anti-Inflammatory, Antioxidant

3.6. Phytosomes containing dosage forms-

Oral and topical administration of phytosome preparations is both options, but to maximize the formulation's bioavailability, it's important to research the dissolution and disintegration times of the dosage forms. Below are some examples of phytosome dosage forms. **(59)**

Hard gelatin capsules: the maximum amount of powder that may be placed within a size 0 capsule, which is typically 300 mg. Although pre-compression can affect the disintegration time, using a piston tamp capsule filling method can enhance the amount of powder that can be put inside a capsule. **(60)**

Soft gelatin capsules: Vegetable or semi-synthetic oils can be utilized for this, with Indiana recommending a granulometry of 100% < 200 μm in the suspension form. **(61)**

Tablets: The best manufacturing method for producing tablets with greater unitary dosages is dry granulation. Due to the negative impact on the phospholipid complex, wet granulation is avoided. It is important to note that if a direct compression process is used, the phytosome complex should be diluted with 60-70 percent excipients in order to maximize its technical properties and obtain tablets with sufficient morphology. **(62)**

Topical product: The emulsion is used for this purpose to obtain the best result from phospholipid complex. A previously created emulsion needs to have a phospholipidic complex spread in a modest volume of the lipidic phase. For the purpose of incorporating the phytosome complex into the emulsion at low temperatures (less than 40°C). **(63)**

3.7. Patents approved on phytosome:

Table 3- list of some patented technologies related to phytosomes

Title of patent	innovation	Patent no.	Ref.
Phospholipid complexes of olive fruits or leaves extracts having improved bioavailability	improved bioavailability	EP/1844785	**(64)**
Complexes of saponins with phospholipids and pharmaceutical and cosmetic compositions Containing them	Complexes of saponins with natural or synthetic phospholipids have high lipophilia and improved bioavailability and are suitable for use as active principle in pharmaceutical, dermatologic and cosmetic compositions	EP0283713	**(65)**
An anti-oxidant preparation based on plant extracts for the treatment of circulation and adiposity problems	Haemorrhoids, varicose veins, arteriosclerosis, phlebitis, and high blood pressure can all be treated using repair made from plant extracts that has an antioxidant effect**.**	EP1214084	**(66)**
Treatment of skin and wound repair with thymosin beta-4	Compositions and methods for treatment of skin utilizing thymosin β4.	US/2007/0015698	**(67)**
Compositions comprising Ginkgo biloba derivatives for the treatment of asthmatic and allergic conditions.	Useful for asthma and allergic condition	EP1813280	**(68)**
Complex compounds of bioflavonoids with phospholipids, their preparation and use, and pharmaceutical and cosmetic compositions containing them	Complex compounds of flavonoids with phospholipids are characterized by high lipophilia and improved bio-availability and therapeutic properties as compared with free, not complex flavonoids.	**US5043323**	**(69)**
An anti-oxidant preparation based on plant extracts for the treatment of circulation and adiposity problems	Treatment for circulation issues such as phlebitis, varicose veins, arteriosclerosis, hemorrhoids, and high blood pressure is based on plant extracts and has an antioxidant impact.	**EP1214084**	**(70)**
Soluble isoflavone compositions	Isoflavone compositions exhibiting improved solubility (e.g., light transmittance), taste, color, and texture characteristics, and methods for Making the same.	**WO/2004/045541**	**(71)**

Fatty acid monoesters of sorbitol furfural and composition for cosmetic and dermatological use	Fatty acid monoesters of sorbitol furfural selected from two different series of compounds in which the side chain is a linear alkyl radical optionally containing at least one ethylenic unsaturation	EP1690862	**(72)**
Oral compositions for the treatment of cellulite	Oral pharmaceutical and cosmetic compositions containing ingredients of vegetable origin for the treatment of cellulite.	US 7691422	**(73)**

3.8. Advantage of phytosomes-

Due to their advantages in the following areas, phytosomes are proving to be promising little spheres for the delivery of phytoconstituents:

- Phytosomes boost the bioavailability of herbs by increasing the absorption of their active components.
- Phytosomes increase bile's solubility in the chemical component, making liver targeting easier.
- Because these carriers promote medication absorption, the adoption of phytosomal drug delivery systems also results in a reduction in dosage requirements.
- Increased stability as a result of the development of a chemical connection between phosphatidylcholine and other bifunctional phospholipid components.
- Use of phytosomes for transdermal medication administration is secure.
- Because phytosomes can move from the hydrophilic environment of an enterocyte cell to the lipophilic environment and then inside the cell, they can be used for systematic targeting.
- By delivering the herbal medication via phytosomes, the nutrient safety of the herbal extracts need not be jeopardised.
- The formulation and ingredients utilized to create phytosomes are safe and thus suitable for use in commerce. Additionally, this technique has a low-risk profile; extensive research has been done on the toxicology of each component.

- A practical and affordable way to deliver skin-protective phytoconstituents in both a calm and stressful setting is using phytosomes. Once more, phosphatidylcholine aids in skin care by nourishing the skin.

3.9. Disadvantage of phytosomes-

Despite having many benefits, phytosomes also have some deadly drawbacks, such as the ability of phospholipids (lecithin) to promote the growth of the MCF-7 breast cancer cell line. Leaching of the phytoconstituents off the phytosome, which lowers the required medication concentration and indicates their unstable nature, is a significant drawback of phytosome. **(74,75)**

2. Phytosomal delivery of herbal extract

For phytotherapeutics to promote patient compliance and prevent recurrent administration, a scientific strategy is required to distribute the components in a novel way. By creating innovative phytosomal drug delivery systems for herbal ingredients, this can be accomplished. Pharmaceutical experts have recently redirected their attention to developing phytosome-containing herbal drug drug delivery systems utilizing a scientific approach**.** One such cutting-edge method that made polyphenolic phytoconstituents more skin permeable and absorbable from the gastrointestinal system was phytosome technology. The flavonoid class of herbal medicines, which includes polyphenolic compounds, has the greatest number of them and they have a wide range of therapeutic uses, including anti-inflammatory, anti-cancer, anti-obesity and many other fields of therapeutics and preventive medicine has been demonstrated by advanced biochemical and pre-clinical research. The market currently sells important herbs in Phytosome form, including Milk thistle, Ginkgo biloba, Grape seed, green tea, Hawthorn, Ginseng, Curcumine, Ammi visnaga, Terminelia root, etc. Undoubtedly, ongoing study and intellectual interaction in the area of this breakthrough technology will speed up efforts to find more potent treatments for serious human maladies. Table 4 lists the results of the numerous phytosome clinical trials and in vitro/ in vitro studies that contained herbal extracts.

Table 4- list of various studies related to phytosomal delivery of herbal extracts

Phytosome	**Herbal extract**	**A study conducted by (year)**	**Findings**	**References**
Greenselect Phytosome	green tea extract	Pierro Di et al (2009)	In obese patients (n=100) of both sexes on a hypocaloric diet, the oral formulation in the form of coated tablets (Monoselect Camellia) (MonCam) containing highly accessible green tea extract was studied. After 90 days of treatment, a significant weight loss and reduced body mass index (BMI) were seen in the herbal extract group (14 kg loss in the green tea group compared to a 5 kg loss in the diet-only group); waistlines were exclusively reduced in male patients. In addition to the impact on weight and BMI, the biochemical indicators of growth hormone, insulin-like growth factor-1, insulin, and cortisol were all improved in both groups.	(67)
Silybin-phytosome	milk thistle (Silybum marianium) extract	Flaig TW et al (2010)	Participants with localized prostate cancer who intended to undergo prostatectomy were welcome. Six volunteers served as controls, whereas six patients received 13 g of silybin-phytosome daily. Although oral bioavailability has improved, prostate tissue buildup has not.	(53)
Silybin-phytosome	milk thistle (Silybum marianium) extract	Lazzeroni M et al. (2016)	This window of opportunity trial was designed to find out, for the first time in patients with early breast cancer, how silybin was distributed throughout the breast tissue. Prior to surgery, 12 breast cancer patients got 2.8 g of silybin-phosphatidylcholine per day for 4 weeks. Oral silybin-phosphatidylcholine can supply significant blood silybin concentrations, which preferentially concentrate in breast tumor tissue. These results serve as the foundation for an upcoming phase II biomarker experiment in the fight against breast cancer.	(34)
Silymarin-phospholipid complex	extract of the milk thistle	Tedesco D et al (2004)	Study focused on the effects of a silymarin-phospholipid complex in reducing the toxic effects of aflatoxin B1 (AFB1) in broiler chickens. Twenty-one 14-d-old male commercial broilers were randomly allotted to 3 groups and treated as follows: basal diet alone [Group C (Control)]; AFB1 at 0.8 mg/kg of feed [Group B1]; AFB1 at 0.8 mg/kg of feed plus	(69)

			silymarin phytosome, a silymarin complexed form with phospholipids from soy, at 600 mg/kg of BW [Group B1+Sil]. our results suggest that silymarin phytosome can provide protection against the negative effects of AFB1 on performance of broiler chicks.	
Allium sativum phytosome	Allium sativum	Nazeer AA et al (2017)	Since Allium Sativum's phenolic ingredient has the ability to both treat and prevent the proliferation of cancer cells, researchers looked into the manufacture of affordable phytosomes of this plant as an alternative to conventional cancer treatments. When the manufactured phytosomes were tested for their impact on cancer cells, it was found that they were 100% hazardous to cancer cell lines. They thus asserted that the allium sativum phytosome had great bioavailability at the tumour site and could also be generalised to active targeting tumour sites by connecting the targeting moiety to the phytosome's surface.	(42)
Momordica Charantia L. andOlea Europaea L. Phytosomes :	Bitter Melon and Olive Leaves extracts	Hamadneh B et.al., (2018)	They looked into the anti-hyperglycemia properties of phytosomes loaded with bitter melon and olive oil extract in hyperglycemic rats caused by glucose. In a 1:2 ratio, phytoconstituents and phospholipid were reacted to create the phytosome. Induced hyperglycemic rats underwent an oral glucose tolerance test to examine the produced phytosomes for hypoglycemic effects. Their findings showed that loaded Phytosomes had stronger antihyperglycemic effects than pure extracts.	(47)
Sinigrin's phytosome	*Brassica nigra* (mustard seeds) extrat	Mazumder A et al (2016)	They investigated Sinigrin's phytosomal formulation anti-cancer properties on A375 melanoma cells while also studying the wound healing activities of Sinigrin on the normal human keratinocytes cells (HaCaT). The results of an in vitro cytotoxic research on normal cells (HaCaT) showed little harmful effects, and the A-375 cell lines significantly preferred the sinigrin phytosome complex over free sinigrin. Investigations on HaCaT cells' ability to repair wounds revealed 50% greater wound closure at different times and concentrations. This study shown that phytosomes loaded with sinigrin	(59)

			might effectively increase the therapeutic effects of phytosomes in cancer therapy and the treatment of cancerous wounds.	
Curcumin phytosomes	Curcumin extract	Purpura M et al (2017)	Twelve healthy human volunteers took part in a cross-over, double-blinded study. Following oral treatment during a 12-hour period, the plasma concentrations of the different curcuminoids found in turmeric (curcumin, demethoxycurcumin, and bisdemethoxycurcumin) were assessed at baseline and at subsequent intervals. it hepatic buildup and increased oral bioavailability of curcumin and Significant plasma level reduction	(73)
Leucoselect - Phytosome	Grape seed extract	Vigna GB et al (2003)	A randomised, double-blind, crossover trial including 24 healthy male heavy smokers who were at least 50 years old was conducted. Phase 1 treatment involved giving 2 capsules twice daily to enrolled individuals for 4 weeks. Each capsule contained 75 mg of a grape procyanidin extract and 75 mg of lactose and soy phosphatidlcholine, which served as the placebo. In a model of oxidative stress (smoking), the polyphenols in grape seed extract have antioxidant properties that may be useful;	(71)

3. Future prospects of Phytosomes

A major method for increasing the therapeutic and pharmacokinetic efficacy of extracts with low bioavailability is the synthesis of phytosomes containing extract or plant active. Researchers have extensively developed the phyto-phospholipid complex as a new drug carrier for systemic activity. A major method for increasing the therapeutic and pharmacokinetic efficacy of extracts with low bioavailability is the synthesis of phytosomes containing extract or plant active. Researchers have extensively developed the phyto-phospholipid complex as a new medication carrier for systemic activity. However, there are still some restrictions on the stability of Phytosomes. Therefore, it is essential to investigate research to address the concerns regarding the preparation method, stability, and actual clinical superiority of these drug delivery systems. For the creation of phyto-phospholipid complexes, hazardous organic solvents are replaced with hydrophilic solvents like ethanol, increasing their

suitability for usage in clinical settings. The yield of the phyto-phospholipid complexes varied significantly between studies, ranging from about 25% to more than 90%. This variation has been linked to various formulation factors, including the ratio of the drug to the phospholipid, the processing temperature, and the processing time, all of which have been shown to affect the yield of the carrier system. Future research projects must take this component of the formulation into account to provide the highest-quality formulation possible. The molar ratios of drugs to phospholipids, along with temperature and other variables, can be optimised using further statistical techniques like factorial design, spherical symmetric designing, and others to get the highest level of entrapment efficiency and the best drug release profile.

4. Conclusion-

This article aims to provide a succinct overview of phytosomes as a delivery method. phytosomes are innovative formulations that increase the bioavailability of hydrophilic flavonoids and other comparable substances through the skin or digestive system. They differ from other traditional formulas in numerous notable ways. Phytosome formulation is a straightforward process that is easily scaled up for commercial use. For this kind of new formulation, the characterisation approaches and analytical tools are well established. For novel phytosome formulations, procedures, and applications, many patents have previously been approved. Phytosome technology has a bright future as far as applications for hydrophilic plant chemicals and formulation technology are concerned.

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