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Phytosomes: The Novel Drug Delivery System

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ABSTRACT:
Nowadays, natural remedies are used to treat the majority of prevalent diseases and nutritional issues. Many extracts as well as phyto components, found to have high bioactivity in-vitro, show little to almost no in-vivo activity due to insufficient lipophilicity, incorrect molecular mass, or both, which results in a lower absorption and bioavailability.Therefore, much effort has been made to design a novel herbal delivery system concept, namely, phytosomes, which are superior to traditional herbal extracts in terms of absorption, use, and outcomes. Plants are referred to as phyto and some as being cell-like. The Phytosomes tiny, cellular structure.Phytosomal complexes were initially researched for cosmetics uses. However, Indena, a well-known provider of nutraceutical substances like milk thistle, ginkgo biloba, grape seed, green tea, hawthorn, ginseng, etc., are created, maintained the PHYTOSOME technique. In addition to being antioxidant, phytosome also reduces inflammation. In India and other countries, phytosome development is still in its infancy. In the fields of medicine, pharmacology, and cosmetics, it has a lot of potential.

KEY WORDS: Phyto-phospholipid complexes, Bioavailability, Phytosomes, Phyto constituents.

I. INTRODUCTION OF PHYTOSOMES:

Indena invented the Phytosome technique to add phospholipids into standardised extracts and optimise their absorption and use. Phytosomes are hydrophilic biologically active phytoconstituents that are more internally and effectively utilised mostly by body than typical herbal extracts. They have an increased herbal complex of active components and phospholipid products.Phytosome was indeed a Greek term where "Phyto" indicates "to plant" and the other term "some" indicates "to be like a cell." Herbal extracts are more bioavailable thanks to Phytosome innovation. It is indeed a bioactive phytoconstituent mixture made up of polar polyphenolics and dietary phospholipids with distinct physicochemical and spectroscopic characteristics.Any herbal product's performance is contingent on the active components being delivered at a sufficient amount. The established health-giving function of the phospholipids itself gives Phytosome an extra depth.

Pharmacokinetics and activity investigations in people and animals have showed that phytosomes have a higher bioavailability than the simpler, non-complexed plant extract. Because of their physiochemical and spectroscopic properties, these chemicals can be regarded as new entities.At the moment, phytosomes are generally employed in cosmetology to transfer chemicals that are dissolved in water towards the epidermis of skin.This method was also beneficial inmedicinal preparations for oral cavity therapy with brief contact durations.

Flavonoids account for the majority of phytomedicine's functional ingredients (e.g.Bilberry anthocyanidins with green tea catechins, milk thistle silymarin). Most of the flavonoids are not good at absorption [1]. Phytosomes are made from water-soluble flavonoid components that have been transformed into lipid-compatible molecular complexes. [2]Phytosomes aren't really liposomes; they differ structurally. The liposome is a combination of several phospholipid bilayer which can encapsulate active Phyto molecules, whereas the phytosome is a combination of numerous phospholipid molecules.

Excessive drug packing, enhanced stability (due to the development of chemical bonding in between phytoconstituent and the hydrophilic head of the amphiphile molecule) [3] and enhanced bioavailability are just a few benefits provided by phytosomes.[4] Furthermore, for polar phytoconstituents, a better adsorption rate results in reduction in dosage of active components required to elicit a biological impact. It primarily safeguards the herbal extract from digestive fluids and germs in the intestines.

Milk Thistle: The First Phytosome:

The flavonoHgnan silybin, the primary ingredient of silymarin, was the basis for the very

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first marketed phytosome production. The milk thistle fruit (Silyhum marianum belongs to the family Asteraceae/Compositae) contains a flavonol compound. IDB 1016 or Silipide [5,6,7] were the original names for this phytosome formulation, which was later renamed Siliphos* PhytosomeTM. [5] Clinical studies have shown that silybinphosphatidylcholine has antioxidising, anti-inflammatory, liver detoxifying nature. [8]

II. MATERIALS AND METHODS

Structure of phyto-phospholipid complexes:

Active components bind with the polar head of phospholipids to create phyto-phospholipid (phytosome) complexes [9]. Phospholipid complexes are formed as a result of connections involving active ingredients and phospholipids. The phospholipid head group is embedded in the complex, but somehow the two long chain fatty acids are not involved. To generate a lipophilic surface, The polarity component of combinations might move and be encircled by the two lengthy fatty acid chains.When diluted in water, phyto-phospholipid complexes form aggregates that mimic a tiny cell which shows similarities to lipid bilayer vesicles. [10]

The significant features of phytosomes were represented in Figure-1, while in the phytosomal structure, the primary substance is a membrane essential component and the molecules are stabilised by hydrogen bonds to the hydrophilic head of the phospholipid molecule.Liposomes are lipid bilayer-based confined vesicles which can enclose substances in an aqueous chamber or multiple lipid bilayers but just don't interact with them [11].

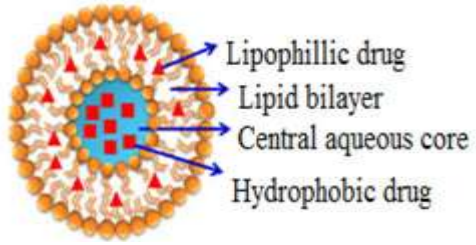

Figure 1. Structural representation of Phytosomes

Components of Phytosomes:

Bombardelli postulated that phytosomeswere formed through reaction of phospholipids with main component derived from plants in a stoichiometric ratio [12]. Phospholipids, phytoingredients, solvents, and the stoichiometric ratio engaged in the making of phytosomes are the four important components [10].

1. Phospholipids –

Egg yolks and seedlings are high in phospholipids. Industrially manufactured phospholipids are presently accessible [10]. Depending on the backbone, phospholipids are classified as glycerophospholipids or sphingomyelins. Phosphatidylcholine (PC), phosphatidylethanolamine (PE), phosphatidylserine (PS), phosphatidic acid (PA), phosphatidylinositol (PI), and phosphatidylglycerol (PG) are all glycerophospholipids [13].

The principal phospholipids used to create complexes with a hydrophilic head group and two hydrophobic hydrocarbon chains are PC, PE, and PS [14]. PC is the most widely employed phospholipid in the synthesis of phospholipid complexes. The amphipathic characteristics of PC provide it with intermediate solubilization in both aqueous and organic environments. PC is also an one of the important structural component of cell, which explains its high biocompatibility and les toxicity. Hepatoprotective properties of PC molecules have been documented in curing of hepatic related illnesses like hepatitis, fatty liver, and liver-cirrhosis [15][16].

2. Phyto-active constituents –

Researchers often characterise the main ingredients of herbal constituents based on in-vitro pharmacological effects rather than in-vivo functions. Polyphenols make up the majority of these chemicals. F or example, Hesperidin is a physiologically active polyphenolic ingredient of plants that has a preference for the aqueous solution and is not able to pass across the biological membranes. Others, such like curcumin and rutin, have significant lipophilic characteristics and not able to disintegrate in gastrointestinal fluids. Phytosomes not only improves the solubilization of lipid polyphenols in water, it can able to improve membrane permeability of polar polyphenols in water.In addition to this, the complex formation helps in the protection of polyphenols from external influences such hydrolysis, photolysis, and oxidation.Any active molecule can be created using the same method, and phytosomes are not just limited to polyphenols. [17]

3. Solvents –

Different investigators have utilised different solvents as the basic solutionto produce the phytosomes.Aprotic solvents like aromatic hydrocarbons, halogen derivatives, methylene chloride and ethyl acetate, or cyclic ethers were

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utilised to produce phyto-phospholipid complex, but protic solvents like ethanol have mainly superseded them [9], [18].Protonic solvents like ethanol, methanol have lately been used to succeed in creating phospholipid complexes. Solvents of many sorts have been thoroughly investigated. Because it leaves behind minimal residue and causes very little damage, ethanol can indeed be widely employed as a solvent whenever the output of phospholipid compounds is large enough.Certain liposomal drug complexes function properly in the contact with aqueous or a buffer solution, in which the phytosomes contact with a low-dielectric-constant solvent [19]. To lower the solubility of a solute in the solvent, a supercritical fluid (typically Carbondioxide) can be used as an anti-solvent.

4. Stoichiometric ratio of phyto active constituents and phospholipids –

In most cases, phytosomes are formed through the reaction of synthetic or natural phospholipid with the main active component in the molar ratio of 0.5 - 2.0 [20]. A stoichiometric ratio of 1:1, on the other hand, is thought to be the most effective for forming phospholipid complexes [21]. Moreover, other active component and phospholipid stoichiometric ratios have already been utilised. Maryana et al. produced silymarin-phospholipid complexes with stoichiometric ratios of 1:5, 1:10, and 1:15 and discovered that the complexes containing stoichiometric ratio of 1:5 had the goodstructural features and largest drug loading of 12.18% ± 0.30% [22].It's not always optimal to use a 1:1 stoichiometric ratio when making phospholipid complexes.The ratio of active components and phospholipids should be altered as per the various objectives for different medications,the highest medication loading, for instance.

III. ADVANTAGES OF PHYTOSOMES:

1. Enhance the bioavailability:

In various research, phytosomes have been observedto enhance the bioavailability and minimise the dosage by increasing the drug absorption through the oralroute. As a result, it has the potential to greatly boost therapeutic efficacy. Permeability nature of the membrane and oil–water partition of main active components enhance dramatically after the development of phytosomes. In comparison to free active components, phyto-phospholipid complexes are more rapidly dissolved and produces more bioavailability. Hence, the synthesis of phyto-phospholipid complexes has grown considerably in recent years.

2. Enhance percutaneous absorption:

Phytosomal constituentsare able to move easily from a hydrophilic area to the cell membrane's lipophilic area into the cell [23]. As a result, many investigations have shown that applying phytoconstituents in the form of phytosomes improves percutaneous absorption [24], [25]. Because of the above skin permeation qualities, phytosome are frequently used in transdermal sector [26], [27].

3. Hepatoprotective effect:

Phosphatidylcholine is a raw substance with significant medicinal potential [28]. Phosphatidylcholine serves as a hepatoprotective as well as a constituent in phyto-phospholipid complexes. As a result, when the patient takes phosphatidylcholine, it has a synergistic impact in protecting the liver. Phospholipids have nutritional benefits in various instances.

4. Some other advantages:

Phyto-phospholipid complexes have a higher drug complexation rate, and their synthesis is simple [29]. Furthermore, phyto-phospholipid complexes have a higher stability due to chemical interactions formed in between theherbal extracts and the phospholipid molecule. Phyto-phospholipid complexes increase liver targeting by enhancing the solubilization of bile to main active component [23]. The drug's duration can be extended in some situations. Because of their limited solubility in water, they can produce stable emulsions or creams.It improves herbal ingredient absorption and thus the bioavailability, resulting in less dosage. Because of their higher skin permeation and lipid profile, they are often employed in cosmetics.

Phytosomal properties:

Physico-chemical properties:[30]

1. A phytosome seems to be a combination that is created when stoichiometric amounts of phospholipids and herbal constituents react with a natural product in a liquid solution.
2. Spectroscopic evidence indicates that the primary phospholipid-substrate combinations results from the hydrogen bond formation between the hydrophilic head of the phospholipids (phosphate and ammonium groups) and the polar functionality of the substrate.

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3. Membrane phospholipids are an essential component.
4. The complex's H1-NMR and C13-NMR spectra can be compared to those of the pure precursors to determine phosphatidyl choline.
5. The combination can dissolve in low polarity liquids because of the phospholipid and flavonoid molecules [31,32].
6. They're lipophilic compounds having high melting point that can easily solubilize in nonpolar solvents (but not in fats) and modestly solvable in fats.
7. Phytosomes take on a micellar shape when exposed to water, generating liposomal-like structures.
8. Phytosomes range in size around 50 nm to a few hundred micrometres. [33]

Biological properties:

1. Phytosomes are innovative herbal preparations that are more easily absorbed, utilised, and thus generate greater outcomes than traditional herbal extracts.
2. Research on pharmacokinetic and pharmacodynamic properties in animal research and healthy human volunteers have shown that the phytosome has a higher bioavailability than non-complexed botanical derivatives [34].

Characterization of phytosomes

1. Solubility and partition coefficient:

Analysing the solubilization in organic, inorganic solvents, and also the n-octanol, water partition coefficient, is really necessary for describing main components, active constituent phyto-phospholipid complexes, and physical mixtures (P).Phytosomes possess higher lipophilicity and hydrophilicity than active components in general, and they usually have greater lipophilicity [10].

2. Particle size and zeta potential:

Particle size, zeta potential are two crucial features that are linked to their stability and repeatability. The typical particle size of phospholipid complexes ranging from 50 nm to 100 m. The complex's average particle size and zeta potential were found to be 153±39 nm and 10.09±0.98 mV. [35]

3. Scanning electron microscopy (SEM) and transmission electron microscopy (TEM):

SEM provided vital information about complexes' solid-state characteristics and surface shape. The transmission electron microscope (TEM) is frequently utilised for the examination of crystallisation and dispersion of nanomaterials, as well as to determine the particle size of nanoparticles. Active chemicals can be seen in a highly crystalline condition using SEM;however, the structured crystals vanish after complexation. TEM revealed that phyto-phospholipid complexes have vesicle-like structures when diluted in distilled water and shaken lightly [35].

Structural verification of Phyto-phospholipid complexes:

1. Ultra violet spectra(UV spectra):

Samples with varying UV absorbance can be utilised to determine their own structural qualities. The properties of components' UV absorbance including during and after the complexation have not been shown to alter in most experiments. When chemicals are mixed with phospholipids, their chromophores are unaffected.

2. Differential scanning calorimetry (DSC):

Through analysis of transition temperature, emergence of new peaks, elimination of previous peaks, melting points, and variations in the relative peaks area in DSC, interactions can be identified [36]. The distinctive peaks of Phyto-phospholipid complexes are frequently very different from those of a physical combination. Strong interactions are believed to result in the active substances, along with the two fatty chains of phospholipids, free rotations are prevented by the polar portion of phospholipids.The rutin and PC peaks vanished from the DSC thermogram, which revealed two distinctive peaks which are lower than those of the physical combination [37].

3. Fourier transform infrared spectroscopy (FTIR):

FTIR is widely used structure analytical approach that produces diverse functional groups with distinct band number, location, shape, and intensity properties. Comparison of phospholipid complex spectra to that of physical mixes can be used to confirm the development of Phyto-phospholipid complexes. Multiple studies may produce various outcomes. The FTIR of rutin and Phyto-phospholipid complexes was mirror images to that of pure rutin [37]. Mazumder et al. found that the FTIR of sinigrin-Phytosome complexes differed from sinigrin, phospholipids, and mechanical mixes [35].

4. X-ray diffraction:

Nowadays, X-ray diffraction is a fantastic method to determine the morphology including crystals and

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amorphous components. It is commonly used to study active ingredients, active constituent phytophospholipid complexes, PCs, and their physical combinations. The X-ray diffraction pattern of an active ingredient and physical mixture reveals dense crystalline peaks, indicating a high crystal form. Active element phyto-phospholipid complexes, on the other hand, show no crystalline peak, implying that the constituents in contact with phospholipids are molecular or amorphous. Active components had lower lipophilicity and hydrophilicity than phyto-phospholipid complexes [10].

5. Nuclear magnetic resonance (NMR):

In order to identify the structural properties of the complexes, techniques like 1H NMR and 13C NMR are used. Hydrogen bonds, but not chemical bonds, are responsible for the connections among the polyphenols and phospholipids. The hydrophobic side of lipids can function to encapsulate the membrane on the central choline-bioactive sections of these complexes, according to the spectra of distinct phyto-phospholipid complexes.

How Phytosome Differ from a Liposome?

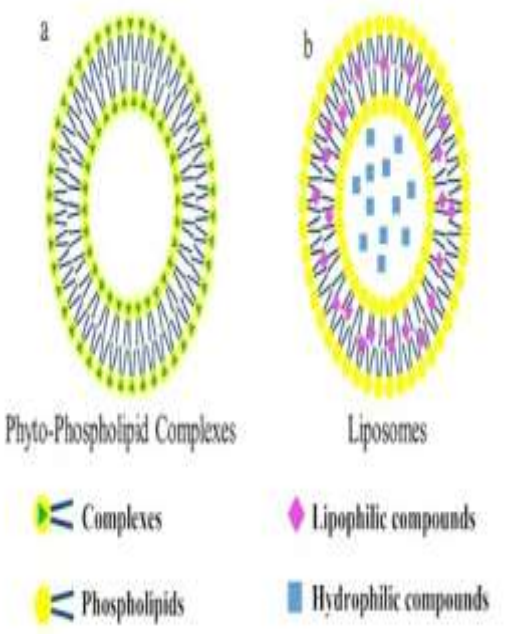

Figure- 2 structural comparision of Phytosomes and liposomes

A lipid bilayer surrounding an aqueous layer forms the liposome which is a small spherical particle. A phytosome is a phospholipid-based compound containing a natural active component. The active components of liposomes are aqueous soluble and are housed in the inside of the cavity.Through polar contacts and hydrogen bonds, the lipophilic guest's polar activities communicate with the charged phosphate head of phospholipids generatesaspecific configuration that can be shown throughspectroscopy [38-43,30].

When it is administered directly to the skin, the Phytosome preparation boosts active substance absorption [32,44-51] and boosts systemic bioavailability when ingested orally. Phytosomes have a micellar form and a spherical shape in water phase, identical to liposomes but with a distinct location. Liposomes are largely utilised in the purpose of cosmetics to distribute aqueous soluble ingredients to the skin. By combining an aqueous soluble chemical with PC, thus the formation of a liposome is done and it includes no formation of a chemical connection. Similarly, based on the composition, the phytosome processes the PC and the various plant components form a 1:1 or 2:1 complex. Because of this distinction, phytosomes penetrate considerably better than liposomes. In beauty products, phytosomes surpass liposomes [30, 52].

Methods of Preparation:

Methods like solvent evaporation, freeze-drying, and anti-solvent precipitation are the three main techniques used for producing phyto-phospholipid complexes. Figure 2 depicts the typical stages of phytosome production.

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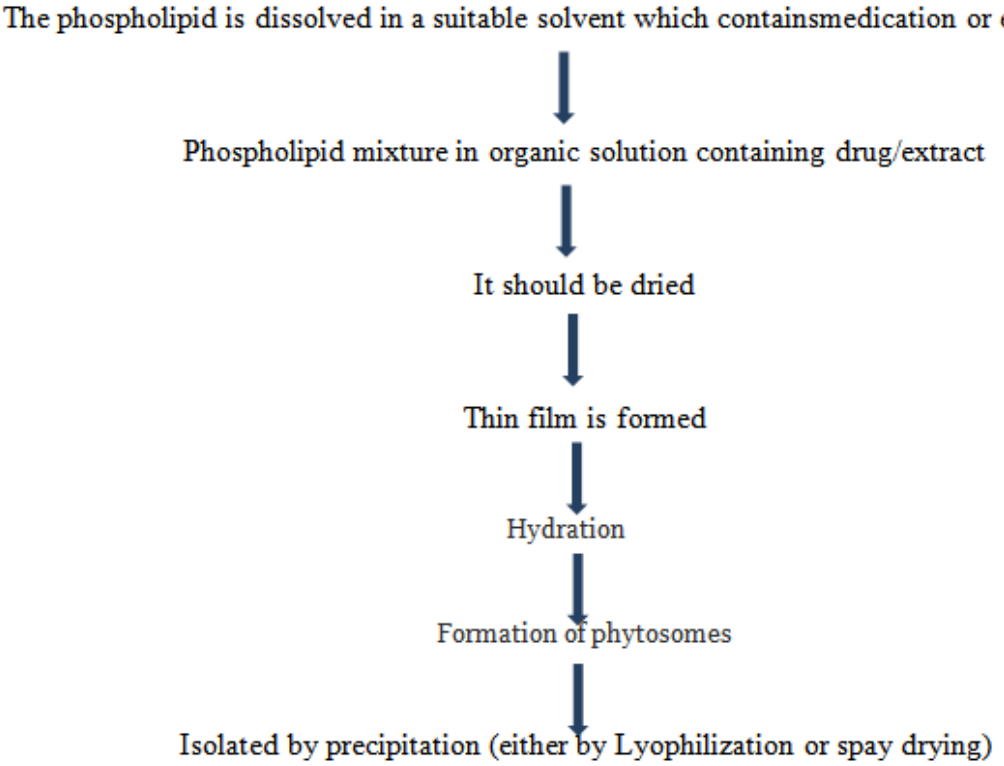

Figure3: Common steps forPhytosomeformation [53]

1. Solvent evaporation method:

To form the phospholipid complexes, solvent evaporation was an oldest and widely used approach. Shan and colleagues prepared oleanolic acid-phospholipid complexes using the solvent evaporation approach [54]**.**A solvent or combination of solvents is used to combine the molecule of interest and the phospholipid. The liquid is then mixed gently for a while before being vaporized in a rotary evaporator[25].The rotary evaporator works on the principle that providing vacuum lowers a solution's boiling point, then rotating the solution to increase the heating surface area. The rota evaporator is a good method for causing complex formation because of its speed and capacity to manage a high volume of solvents. However, in order to achieve the requisite boiling point depression when evaporating high boiling point solvents such as DMSO and DMF, for this a high-pressure vacuum system is required.

2. Mechanical dispersion method:

The phospholipid is mixed in a solution and then sonicated tillcertain time period in the mechanical dispersion process. The drug solution is then continually introduced drop by drop slowly into the solution while sonication is performed.

3. Super critical fluid process:

SCF methods are widely used because it can create particles with a precise size and dispersion. This procedure can be carried out in low-temperature and low-pressure environments. In addition, it is more environmentally friendly than processes that use organic solvents. The most frequently used supercritical fluid is carbon dioxide, which has a critical temperature of 31°C and a critical pressure of 74 bars, which is employed at mild temperatures (40–60°C).However, there are several drawbacks to this approach, such as the low solubility of polar molecules in supercritical solvent (Carbondioxide). Li et al. [55] used this method to produce puerarin phospholipid complexes and compared it to other methods such as solvent evaporation, freeze drying, and gas anti-solvent crystallisation. They reported that the phospholipid complex created using supercritical fluid technology had a stronger ability to cause amorphization of the medication than the other three ways, resulting in better dissolving efficiency.

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4. Co-solvent lyophilization:

The lyophilization procedure is based on the sublimation concept (release of water without the need for a liquid phase from a frozen state). Lyophilization occurs at a temperature and pressurewhich is below triple point, allowing ice to sublimate. The freezing stage, primary drying, and secondary drying are all processes in the lyophilization process. Cui et al. [56] provide an example of the use of co-solvent lyophilization to produce drug-phospholipid complexes.

5. Anti-solvent precipitation:

Both drug, phospholipid is mixed in an organic solvent and mixed gently for a set amount of time before being precipitated with anti-solvent, which has a poor solubility for the created complex. Anti-solvent precipitation can be done at room temperature and pressure without the need for costly technology. The authors used an anti-solvent precipitation approach to precipitate an ellagic acid phospholipid complex utilising DCM as the solvent and n-hexane as the anti-solvent.

Factors influencing the Phytosome formation:

Orally and topically prepared phytosome complexes are available in the market. Solvent, stoichiometric ratio of active ingredients, reaction temperature, and reaction duration are the most important parameters that determine the synthesis of phyto-phospholipid complexes. Various process factors can be specified depending on the intended outcome. Saoji et al. investigated the effects of process variables including the phospholipid-to-drug ratio, reaction temperature, and reaction time on yield, and employed a central composite design to find the best formulation [57]. Das and Kalita produced a rutin Phytosome in various stoichiometric ratios for optimal solubility and skin penetration [58]. According to a recent publication [59], the maximum output of apigenin-phospholipid complexes can be generated by changing stoichiometric ratios and temperature of the reaction.

Applications of Phytosomes:

Phytosomes have been studied for their medicinal potential, particularly their capacity to increase the bioavailability of polar phytoconstituents. Phytosomes are used to treat a variety of ailments, including liver disease, heart disease, and others. Anti-inflammatory, lipolytic, vasokinetic, anti-edema, and other uses for phytosomes are just a few of them. It's also employed as a nutraceutical, immunomodulator, antioxidant, and other things. [60]

1. Phytosome penetrates nonlipophillic plant extracts, increasing their bioavailability.
2. Phytosomes are frequently utilised in cosmetics due to their superior skin penetration. They act in small amounts to get desired results.
3. Because of their high absorption, Phytosome can be used to provide liver-protective flavonoids.
4. Small cells created by the phytosome mechanism protect the pricey constituents of the leaf extracts from degradation brought on by digestive fluids and intestinal microorganisms.
5. Anti-inflammatory formulations, medicines, and cosmetic formulations all contain phytosomes. Acute and chronic liver disorders can be treated with phytosomes.
6. In addition to these uses, phytosomes can be used as an antioxidant, brain stimulant, immunomodulator, skin-improving agent, anti-aging supplement, antihypertensive agent, and for a variety of other purposes [61].

IV. RESULTS AND DISCUSSION:

Table-1 Distinct phytosome on the market have different therapeutic applications [62, 63, 64, 65].

Phytosomes	Phytoconstituents complex	Indication
Greenselect phytosome	Epigallocatechin 3-O-gallate from cameliasinensis (green tea)	Used as an antioxidant in the body, cancer protective and cholesterol damage.
Ginkgoselect phytosome	It constitutes 24 % ginkgo flavono glycosides from Ginkgo biloba	Used mostly for the adults over the age of 50, this is the best option. It protects the linings of the brain and blood vessels [66].
Silybin phytosome	It includes Silybin from silymarin (milk thistle)	If you need extra antioxidant protection for your liver or skin, this is the best option.
Hawthorn phytosome	Flavonoids	It is the best choice for heart disease

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Glycyrrhiza phytosome	18-beta glycyrrhetinic acid	Anti-inflammatory Activity [67]
Curcumin (Merinoselect)	Polyphenol from curcuma longa	It is the cancer chemopreventive agent which improves the oral bioavailability of curcuminoids and the plasma
Grape seed (Leucoselect)	Procyanidins from vitis vinifera	It is used as an anti-oxidant, anticancer agent

V. CONCLUSION:

The use of herbal extracts is limited because of less bioavailability and absorption after oral administration. As a result, phytosomes are a novel technique that can aid in improving absorption and bioavailability. It enhances the herbal extract's stability. Novel drug delivery systems, such as phytosomes, serve to boost therapeutic value by minimising toxicity, as well as reducing the number of times medications are administered.Phospholipid-based drug delivery systems have shown promise for better and more efficient medication delivery.Phytosomes are a type of phospholipid-based drug delivery system that has a higher absorption rate and stability profile than liposomes and other phospholipid-based drug delivery systems. Phytosomes are currently utilised mostly in cosmetics to transfer water-soluble compounds to the skin. The technology is capable of delivering the substance both topically and orally. Phytosomes serve as a link between traditional drug delivery and new drug delivery systems. Many more phytosome benefits in terms of therapeutic formulations will be discovered in the upcoming yrs. Phytosomes are used as a pharmaceutical and have a wide range of applications in medical field.

CONSENT

It is not applicable

ETHICAL APPROVAL

It is not applicable

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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