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Review Article

Phytosomes: A Comprehensive Review on Advances Herbal Drug Delivery Systems

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ABSTRACT

Herbal extracts often exhibit poor bioavailability due to limited solubility, instability, and rapid metabolism, restricting their therapeutic potential. Phytosomes, a novel vesicular delivery system based on the complexation of phytoconstituents with phospholipids, have emerged as an effective approach to enhance the absorption and clinical efficacy of plant-based molecules. This review discusses the concept, preparation techniques, characterization parameters, and pharmacokinetic advantages of Phytosomes. Recent advances in herbal drug delivery, including improved therapeutic outcomes for flavonoids, terpenoids, polyphenols, and saponins, are highlighted. Furthermore, challenges associated with scale-up, stability, and regulatory acceptance are critically examined. The review concludes that phytosome-based delivery systems represent a promising strategy to enhance the performance of herbal medicines and support their translation into clinically effective formulations.

INTRODUCTION

Phyto" indicates plant and "some" implies cell like. Phospholipids and the phytoconstituents form an H-bond, which improves the physical stability of Phytosomes and increases the absorption of hydrophilic polar phytoconstituents, increasing their bioavailability and therapeutic effects. Phytosomes also known as Herbisomes. Herbosome is the novel emerging technique applied to phyto-pharmaceutical for the enhancement of bioavailability of herbal extract for medicinal applications. The phytoconstituents have pharmacological activities such as anti-tumor, anti-inflammatory, antinociceptive, anti-obesity, thermoregulatory effects, cardioprotective, anti-asthmatic, antidiabetic, anti-oxidant, hepatoprotective and potent CNS activities. (1) Numerous plant compounds with diverse biological activities and health-promoting

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Sericoside herbosome as an anti-wrinkle and tonic, ginkgo select herbosome as an antioxidant and cognitive enhancer, hawthorn herbosome for cardiovascular health, and "Meriva," a curcumin herbosome for healthy joints. Because of its broad phytochemical profile, the purified olive fruit extract was used to create the Oleaselect phytosomes. This extract has anti-hypertensive, diuretic, antiatherosclerotic, antioxidant, and hypoglycemic qualities. (2) The phytosomes significantly enhance these polar active ingredients' bioavailability. A few of the phospholipids identified in Phytosomes preparation consists of egg lecithin, soy phospholipids, such as phosphotidylcholine. The lipid is easily traversed by phytosomes. bio membranes, which are said to boost the bioavailability of of extracts that are weakly lipid soluble by boosting the absorption in digestive system. The phytoconstituents include some Included in phytosomes include ginkgo biloba extracts, olive oil, milk thistle, hawthorn, grape seed, and green tea, Ginseng, etc. (3) A well-known producer of pharmaceuticals and nutraceuticals created the patented phytosome technology, which involves adding water-soluble phytoconstituents or standardized plant extracts to phospholipids to create lipid-compatible molecular complexes known as phytosome Phyto-constituents from herbs that are encased in phospholipids. Because phosphatidlcholine has a gastro-protective quality, the Phytosome method creates a tiny microsphere or cell that shields the plant extract or its active ingredient from being broken down by stomach secretion and gut bacteria. (4) Herbal medicines known as phytosomes are packaged in nanoscale vesicles plant extracts with anxiolytic qualities have been investigated in a variety of formats, including standardized extracts and traditional herbal formulations. Among these herbs are valerian (Valeriana officinalis), kava (Piper methysticum), ashwagandha (Withania somnifera), and passionflower (Passiflora incarnata). The sedative and anxiolytic properties of these herbs have led to their traditional use.Taking into account that Phytosomes are mostly used to treat anxiety,Terpenoids, alkaloids, and polyphenolic compounds are the three main categories into which phytochemical components (5) It has been established that natural bioactive substances are effective, secure, and reasonably priced chemotherapeutic medicines. More than 60% of the anticancer drugs presently in use come mostly from natural sources, especially plants side-effect-free cancer treatments . However, stability and limited absorption rates present a hurdle for the use of phenolic compounds it has been demonstrated that encapsulation techniques in drug delivery systems enhance the bioavailability and anticancer effectiveness of bioactive substances, such as phenolics (6) Additionally, phospholipids are used as natural digestive aids and as carriers of nutrients that are both water- and fat-miscible Phytosomes can readily pass through the stratum corneum layer of the skin3 and the lipophilic pathway of the enterohepatic cell membranes.(7) nanosystem types would be employed in theranostics, disease imaging, or treatment.45 The most popular nanocarriers for phytochemicals are vesicular drug delivery systems, which have spherical structures encasing active compounds.(8)

Physicochemical and Biological Properties of Phytosomes

Phospholipids and a natural product combine to form Phytosomes. Stoichiometric concentrations of phospholipids and the substrate react in the right solvent to form such a complex. fatty chain's signals have hardly changed. These findings suggested that the active substance is encased in a lipophilic envelope formed by the two long aliphatic chains, protecting the phospholipid's

polar head and active ingredients (9). Phytosomes are sophisticated herbal medicines that work better than traditional herbal extracts because they are more easily absorbed and used. Pharmacokinetic investigations or pharmacodynamic tests in experimental animals and human subjects have shown that the phytosome has a higher bioavailability than the non-complexed botanical derivatives (10).

Advantages

1. Because the complex form of phytoconstituents has a higher bioavailability, the dosage of phytoconstituents is decreased.
2. The action's duration is extended
3. Herbosomes are easy to produce.
4. Phospholipids and phytoconstituents work together to make gastric secretions more stable and less susceptible to the effects of gut bacteria
5. Phytoconstituents' increased capacity to pass across cellular membranes.
6. Better absorption of lipid insoluble polar phytoconstituents through various pathways results in noticeably greater therapeutic benefits.
7. In addition to serving as a carrier, phosphatidylcholine, which is employed to make herbosomes, has a number of medicinal benefits and has a synergistic effect. (11)

Merits of Phytosomes in Conventional Drug Delivery System

The planterosomal system is non-invasive, passive, and potentially ready for quick commercialization. Because the primary ingredient is better absorbed, a lower dose is needed. The plantersomes show a greater stability profile because of the chemical connections that are formed between the phosphatidylcholine atom and the herb's phytoconstituent. There is a lower dose requirement. Increased efficiency of trapping. Drug distribution to the tissue was guaranteed by planterosomes. When it comes to skin care products, planterosomes are better than liposomes. Planterosomes' poor solubility in aqueous media enables the creation of stable creams and emulsions (13).

Role of Phytosomes in Various Diseases

Covid-19

An immunological response initiates the early stages of COVID-19, which are followed by a second phase in which a cytokine storm and macrophage activation take place. Proteins implicated in the COVID-19 infection cycle can be inhibited by quercetin. (14)

Migraine

Although curcumin has limited effectiveness because of poor absorption, it can be useful in managing migraine attacks. Phytosomal curcumin reduces oxidative stress and neuroinflammation, which in turn reduces migraine in patients, due to its high bioavailability and ability to penetrate the blood-brain barrier (15).

Asthma

A phytosome called Casperome is used to treat Asthma. In order to assess the decrease in frequency between the treatment group and the control group, the patients received inhalational therapy twice daily throughout the trial (16).

Bowel Inflammation

Anaemia, malaise, watery stools, blood in stools, cramps, diffuse intestinal pain, and a reduction in white blood cell count were all less common in the supplemented group. Furthermore, fewer medical

tests and supplementary prescription drugs were required (17).

Ischemic Stroke

Phytosomes comprising mulberry fruit and ginger rhizome extracts reduce inflammation and oxidative stress. It was investigated how phytosomes containing extracts from ginger and mulberry fruit could prevent ischemic stroke (18).

Cancer

Breast cancer accounts for one-fourth of all cancer cases identified in females, making it the most common cancer diagnosed globally. In 2020, there were 2.3 million new instances of breast cancer and about 685,000 deaths from the disease; by 2040, there would likely be more than 3 million new cases and 1 million fatalities (19)**.**

Properties of Phytosomes

Green tea

Due to its many benefits, such as its natural origin, broad dose range, lack of grace period, and appetite-stimulating properties, the use of natural materials derived from plants to treat coccidiosis has become a novel and promising Along with caffeine and L-theanine, green tea is a variety of tea plant (Camellia) caffeine and L-theanine, green tea is a variety of tea plant (Camellia sinensis) that has high quantities of polyphenols.green tea has anticoccidial properties. It Reduce toxic effects and increase bioavailability (20).

Sonneratia alba

Naphthoquinones, flavonoids, tannins, and saponins are the secondary metabolites of Sonneratia alba extract that primarily contribute to its antimalarial activity, with naphthoquinone serving as the principal active ingredient. Nevertheless, its efficacy is restricted by its limited bioavailability. A vesicular system based on phytosomes was suggested as a way to enhance this. In order to improve its antimalarial activity, this work concentrated on creating a phytosome using S. alba and creating a predictive model (21).

Dioscorea nipponica

The ability of various herbal products to prevent obesity. For instance, it was discovered that Dioscorea nipponica had an anti-obesity effect when administered as an oral emulsion,2 that Gambi-hwan extract (22).

Glycyrrhetinic acid

The active principle component of licorice, demonstrated a significant reduction in subcutaneous thigh fat thickness when applied topically, and topical administration of capsaicin, a major component of chillies, was found to have a local antiobesity effect. The soybean Glycine max (L.) Merrill family Fabaceae was found to have a substantial impact on controlling body weight due to its high levels of phosphatidylcholine (PC), protein, and saponin (23).Glycyrrhizic acid's potassium and calcium salts combine to form glycyrrhizin. Glycyrrhizic acid's ammonium salt is called diammonium glycyrrhizinate (DG). It has been shown that licorice saponins promote high levels of humoral (24). This nanotechnology is a technique for the creation of new formulations since phytosomes improve polyphenolic chemicals derived from herbs that are used to treat a variety of illnesses. silver and other metallic inorganic nanoparticles have also been employed as phytocompound nanocarriers (25).

Grape seed extract Vitis vinifera

Grape seeds provide notable protection against the cardiovascular system and other organs by increasing total antioxidant capacity, stimulating physiological defenses of plasma, protecting against ischemia/reperfusion-induced heart damage, and having protective effects against atherosclerosis (26).

Mulberry fruit and ginger rhizome

It has been demonstrated that phytosomes comprising mulberry fruit and ginger rhizome extracts reduce inflammation and oxidative stress. It was investigated how phytosomes containing extracts from ginger and mulberry fruit could prevent ischemic stroke (27).

Hinokitiol

A naturally occurring tropolone molecule obtained from Cupressaceae plants, hinokitiol has attracted significant interest because of its wide range of pharmacological actions, which include strong antibacterial, antioxidant, anti-inflammatory, and anticancer effects (28).

Application of Phytosomes

1) Improving the Bioavailability.
2) Transporting big, varied medications, such proteins and peptides.
3) Secure composition.
4) The efficiency of drug entrapment is improved Phytosome technology.
5) Because of active ingredient absorption is enhanced, a lower dose is needed.
6) When hepatoprotective compounds are utilized, soy phosphatidylcholine, which is used to prepare Phytosomes, also has hepatoprotective properties and has synergistic effects.
7) Herbosomes enhance phytoconstituents' percutaneous absorption.
8) Accepted for use in pharmaceutical and cosmetic applications.
9) A profile of low risk.
10) Toxicological characteristics are well-established.
11) Strong market appeal (29,30).

Table 1. Products with bioactive phytochemicals derived from Phytosomes that are sold.

Phytosome formulations	Source plant	Functions	Reference
Silybin	Silymarin marium	Hepatoprotective and antioxidant activities	31-32
Ginkgo	Ginkgo biloba	brain and vascular protection	33-34
Olive oil	Europae	Anti-Inflammatory, antioxidants, antihyperlipidemic activities cardiovascular protection	35
Centella	Centella asiatica	Vein and skin disorders	36
Greenselect	Camellia silensis	Antioxidant activity	37
Rutin	Ruta graveolens sophora japonica	Rheumatoid arthritis	38
Curcumin	Curcuma longa	Hepatoprotective activity	39-40
Leucoselect	Vitis vinifera	Antioxidant activitiey	41
Ecdhinacea	Echinacea augustifolia	Immunomodulator	42
Cartaegus	Cartaegus Mexicana	Antioxidant	43
Haw thorn	Carteagus specie's	Antihypertensive activity	44
Roscugenin	Ruscus aculeatusan	Antinflamontory	45

Methods and Preparation Techniques of Phytosomes

Phytosomes are primarily prepared by complexing the active phytoconstituents with phospholipids, usually phosphatidylcholine, to form a stable lipid-compatible molecular complex. Several preparation methods are widely reported

Solvent Evaporation Method

Both the herbal extract or isolated phytoconstituent and phospholipid are dissolved in organic solvents like ethanol, chloroform, or dichloromethane. The mixture is refluxed or stirred to allow complexation, followed by evaporation of the solvent under vacuum to form a thin film or dried complex layer. This film can be hydrated to form vesicular structures. The method is simple and effective but can be time-consuming and may expose compounds to oxidative degradation during evaporation.

Anti-Solvent Precipitation Method

The phospholipid-phytoconstituent mixture is prepared in a volatile organic solvent and then added to a non-solvent such as n-hexane under stirring, causing the complex to precipitate due to polarity differences. The precipitate is collected, filtered, and dried for use.

Thin-Layer Hydration Method

The complex components are dissolved and spread as a thin lipid film by solvent evaporation, which is subsequently hydrated with aqueous media. Further processing steps such as sonication or extrusion are applied to reduce vesicle size and enhance uniformity. (46,47)

Evaluation Of Phytosomes

1. Visual Appearance

Assesses color, clarity, uniformity, and presence of aggregates. Ensure batch uniformity and proper dispersion.

2. Particle Size, Size Distribution, and PDI

Measured using Dynamic Light Scattering (DLS). Particle Size: Usually 100–500 nm. PDI: < 0.3 indicates mono dispersity. Significance: Affects absorption, stability, and release profile. (new)

3. Drug–Phospholipid Interaction / Complex Formation Techniques

(a) FTIR (Fourier Transform Infrared Spectroscopy)

Confirms complex formation via: Shifts in peaks of phospholipid head groups Disappearance/ modification of extract functional groups. The chemical makeup and bonding of the two components can be better understood by using FTIR analysis to examine the interaction between the plant extract and phospholipids in the Phytosomes formulation.

(b) NMR (^{1}H-NMR, ^{13}C-NMR)

Provides structural information. Validates chemical bonding between phytoconstituent and phosphatidylcholine.

(c) DSC (Differential Scanning Calorimetry)

Shows disappearance or shift of peaks indicating complex formation.

(d) XRD (X-ray Diffraction)

Shows reduced crystallinity after complexation.

4. Entrapment Efficiency (EE%)

Measures amount of phytoconstituent successfully complexed. Typical methods: Centrifugation,

dialysis. Formula: EE% = (Amount of drug in Phytosomes / Total drug added) × 100.

5. Surface Morphology

SEM (Scanning Electron Microscopy) Shows shape (round/oval), smoothness, and aggregation.

TEM (Transmission Electron Microscopy) Provides nano structural arrangement and shape.

6. Solubility and Dissolution Studies

Measures improvement in solubility due to phospholipid complexation. Use of buffer, water, and simulated gastric/intestinal fluids.

7. In-Vitro Release Studies

Usually conducted via: Dialysis bag method Franz diffusion cell Provides release kinetics (Higuchi, Korsmeyer–Peppas, zero/first-order

8. Pharmacokinetic studies'

In vivo studies can assess the pharmacokinetic profile of phytosomes, which include the distribution, metabolism, excretion, and absorption of the active ingredients in comparison to traditional herbal extracts. Pharmacodynamics studies the biological impacts and therapeutic effectiveness of phytosome formulations in pertinent animal models or clinical trials is known as pharmacodynamic assessment. (48-52)

9. In vitro and in vivo evaluations

In vitro and in vivo evaluations the qualities of them edication, its primary phytoconstituents, which are coated in a phospholipid layer, and the justification for the choice of the specific animal model for testing have an impact on both the in vitro and in vivo evaluations (53,55).

10. Potential Zeta

The phytosome's surface charge is measured by its zeta potential. It is an important parameter that affects the final product's performance and stability. An argon laser is used in a zeta sizer. To determine the phytosome complex's zeta potential, dilute the sample with the solvent before mounting it onto the zeta sizer. Phytosome stability over time is indicateS by a larger zeta potential value. Millivolts (mV) are used to denote it (56)

11. Stability studies

The physical and chemical stability of Phytosomes during various storage circumstances, such as temperature, humidity, and light exposure, can be assessed via accelerated stability testing (57).

CONCLUSION

Phytosomes represent a promising approach to enhance the bioavailability and therapeutic potential of plant-based bioactive compounds. By forming complexes between phospholipids and phytoconstituents, phytosomes improve solubility, absorption, and stability compared to conventional herbal extracts. This technology bridges the gap between traditional herbal medicine and modern drug delivery systems, offering improved pharmacokinetic and pharmacodynamic profiles. With increasing research and advancements in formulation techniques, phytosomes hold great potential for developing effective, safe, and standardized herbal formulations in the future.

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