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Converting the Botanical Products into Therapeutically Active Compounds: The Emerging Roles of Phytosome-Based Delivery System

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ABSTRACT

Introduction: The phytoconstituents have been shown to have a wide range of biological functions with pharmacological implications. However, these phytoconstituents' bioavailability is restricted due to poor absorption. The failure of these constituents to access their site of operation before being degraded, as well as their inability to migrate through the small intestine owing to their multi-ring structures and the lipid composition of the intestinal wall, are the main causes of inadequate absorption. Phytosome technology is one of these devices, which incorporates phospholipids into the uniform active ingredients of herbal extracts, effectively increasing the bioavailability of water-soluble phytoactive constituents including flavonoids, phenolics, and hydrophilic compounds.

Aim: The aim of the study involves highlighting the latest developments in the area of phytosome drug delivery systems which will help researchers in better understanding the subject.

Materials and Methods: Normal databases such as Scopus, PubMed, Google Scholar, and others were combed through to find critical published facts in the form of research articles. Results: This research overview summarizes recent developments in phytosome science, focusing on fundamental principles, characterization techniques, method of development, pharmacotherapeutic uses, marketed drugs, and phytosomes potential prospects.

Conclusion: Phytosomes are a form of advanced herbal extract that is more easily absorbed and produces better results than traditional herbal extract. Phytosomes also improved pharmacokinetic and pharmacological parameters, allowing them to be utilized in the treatment of a variety of diseases. The absorption of phytosome in the gastrointestinal tract is significantly higher than that of the individual portion, resulting in a higher plasma level.

Key Words: Phytosomes, Phytoconstituents, Herbal Extracts, Delivery System, Products, Mechanisms

INTRODUCTION

For hundreds of years, herbal remedies have become the synthesis of medicinal interactions of thousands of practising physicians in indigenous forms of medicine. Traditional medicine, which includes herbal medicines, has recently been identified by the World Health Organization (WHO) as medical procedures that have existed for hundreds of years before the advent and dissemination of modern medicine and are still in use today.[1] Herbal medication are traditional medicines that are mainly used as medicinal plant preparations for therapeutic purposes. Phytotherapeutic agents or phytomedicines are other terms for herbal drugs. These phytomedicines are often available as generic herbal formulations, which are used in several countries and comprise complicated mixtures of one or more herbs.[2]

Medicinal plant usage for health purposes dates back thousands of years and is now used in China, Egypt, India, and other developing countries. Despite major advances in medical medicine and pharmaceutical science, the usage of herbal plants has been an integral part of everyday life in the western world over the years.[3] The number of medicinal plant applications has grown as our understanding of metabolic processes and plant impact on human physiology has grown. According to the World Health Organization, 4 billion people, or around 80% of the world's population, use herbal medicine for any form of primary health care. Major pharmaceutical firms are presently doing comprehensive studies

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into the therapeutic benefit of plant materials collected from rain forests and other locations.[4] A significant proportion of commercial drugs used currently for the prevention of heart failure, high blood pressure, nausea, asthma, and other conditions are now based on substances obtained from plants. Traditional Chinese herbalism, which is part of Traditional Oriental Medicine, Ayurvedic herbalism, which is derived from Ayurveda, and Western herbalism, which originated in Greece and Rome and extended to Europe, North America, and South America, are the three basic systems of herbal medicine.[5] Any Ayurvedic herbs may help with cholesterol, diabetes, and other ailments. Herbal drugs have stood the test of time because of their effectiveness, potency, cultural acceptability, and lack of negative side effects.[6]

Plant preparations or portions of plants have been commonly used in traditional medicine since ancient times, and phytomedicines are also widely used by the majority of the world's population today. Chemical and pharmacological experiments on a variety of plant extracts have been conducted during the past century to determine their chemical makeup and validate conventional medicine indications.[7] The isolation and purification of the different components of an extract have frequently been found to result in a partial loss of specific action for the distilled product. Phytochemical and phytopharmacological sciences have identified the formulations, biological processes, and health-promoting benefits of a wide range of botanical products over the last century.[8] The majority of biologically active plant components are polar or water-soluble molecules. Water-soluble phytoconstituents (such as flavonoids, tannins, glycosidic aglycones, and others) are poorly absorbed, either because of their broad molecular scale, which prevents passive diffusion or because of their low lipid solubility, which severely limits their capacity to migrate through lipid-rich biological membranes, resulting in poor bioavailability.[9] The separation and purification of an extract's constituents have frequently been found to result in a partial or complete lack of real biological activity for the distilled constituent - the normal constituent synergy is lost, most likely due to the elimination of chemically associated compounds that contribute to the active principle's synergistic impact(s). The chemical complexity of the crude or partly distilled extract seems to be crucial for the active constituents' bioavailability.[10] Any constituents of extracts can be lost in the gastric system as ingested orally. Because of the above factors, low bioavailability also restricts the therapeutic usefulness of standardized extracts. Plants are endowed with a plethora of therapeutic and health-promoting compounds, the majority of which are secondary metabolites, the flavonoids becoming the most popular. Flavonoids are commonly found in plants and were first noted for their antioxidant properties. More than 4,000 naturally occurring flavonoids with various biological activities have been reported from plant sources to date.[11]

PHYTOSOMES

Phytosome is a proprietary technology produced by a leading drug and nutraceutical producer for incorporating uniform plant extracts or water-soluble phytoconstituents into phospholipids to create lipid-compatible molecular complexes known as phytosomes, which greatly increase absorption and bioavailability.[12] 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.[13] Phytochemical and phytopharmacological sciences have identified the formulations, biological processes, and health-promoting benefits of a wide range of plant products over the last century. Phytosomes also improved pharmacokinetic and pharmacological parameters, making them useful in the management of acute and chronic liver failure caused by poisonous metabolic or infectious agents, as well as degenerative diseases.[14] It also has anti-inflammatory properties and can be found in medicinal and cosmetic formulations. Soy phospholipids are combined with botanical derivatives in an appropriate solvent to produce phytosome. These complexes may be classified as novel entities based on their physical-chemical and spectroscopic properties.[15] Table 1 highlights some commercially available biologically active Phytosomes products.

Table 1: Some common Phytosomes products and their therapeutic applications.

Phytosomes Products	Phytoconstituents	Indications
Aesculus Phytosomes®	Escin	Anti-edema
Bilberry Phytosomes®	Anthocyanosides	Improve capillary tone, reduce abnormal blood vessel permeability, and Anti-oxidant
Boswellia Phytosome®	Boswellic acid	Anti-inflammatory
Centella Phytosome®	Terpenes	Vein and Skin disorders
Curcuma Phytosome®	Curcumin	Anti-oxidant, Anti-cancer
Echinacea Phytosome®	Echinacosides	Immunomodulator
Embelia Phytosome®	Quinone	Anti-bacterial, Anti-fertility
Grape Seed Phytosome®	Procyanidins	Cardio-protective, Systemic anti-oxidant

Table 1: ***(Continued)***

Phytosomes Products	Phytoconstituents	Indications
Ginkgo Phytosome®	Ginkgo flavonoids	Protects the brain and vascular linings, Anti-skin ageing
Ginseng Phytosome®	Ginsenosides	Immunomodulator
Glycyrrhiza Phytosome®	Glycyrrhetinic acid	Anti-inflammatory, the Skin whitening agent
Green Tea Phytosome®	Epigallocatechin 3-O-gallate	Systemic anti-oxidant, Onco-protective
Hawthorn Phytosome®	Flavonoids	Nutraceutical, Cardio-protective, Anti-hypertensive
Melilotus Phytosome®	Melilot	Venouscirculatory disturbance, Bruises, and Sprains
Olea Phytosome®	Polyphenols	Cardio-protective, Anti-oxidant
Olive oil Phytosome®	Polyphenols	Antioxidant, Anti-inflammatory, Anti-hyperlipidemic
Palmetto berries Phytosomes®	Fatty acids, alcohols, and sterols	Non-cancerous prostate enlargement
Panax Ginseng Phytosome®	Ginsenosides	Food product
Pterocarpus Phytosome®	Marsupin, Liquiritigenin, Pterosupin	Anti-diabetic, Anti-viral
Ruscus Phytosome®	Varicose	Improve capillary tone, reduce abnormal blood vessel permeability, and Anti-oxidant
Sericoside Phytosome®	Sericosides	Skin improver
Sophora Phytosome®	Quercetin	Anti-oxidant, Anti-inflammatory
Super Milk thistle Extract Phytosome®	Silybin	Anti-oxidant for liver and skin
Terminalia Phytosome®	Sericosides	Anti-wrinkles, Capillary protecting, Anti-inflammatory, Anti-edema
Vaccinium Phytosome®	Antcinocide	Anti-oxidant, Improve capillary tone
Visnadine Phytosome®	Visnadine	Circulation improver
Vitis Phytosome®	Naringenin	Hepatoprotective, Anti-inflammatory, Anti-tumor
Zanthoxylum Phytosome®	Alkylamides	Anti-itching, Soothing agent

COMPONENTS OF PHYTOSOMES

Flavonoid and terpenoid components of plant extracts (such as (+) catechin, (-) epicatechin, 3-rhamnoside, apigenin-7-glucoside, diosmine, hyperoside, luteolin, luteolinglucoside, kaempferol, quercetin, quercretin-3, quercetin-3-rhamnoside, rhamnoglucoside, vitexine, etc. The reaction of a stoichiometric sum of the phospholipid (phosphatidylcholine) with a uniform extract or polyphenolic constituents (such as basic flavonoids) in a non-polar solvent produces phytosomes (**Figure 1**).[16] Molecules are anchored to the polar choline head of the phospholipids by chemical bonds, as shown by spectroscopic techniques. The unit phytosome is normally a flavonoid molecule bound to at least one phosphatidylcholine molecule, according to precise chemical examination. As a consequence, a tiny microsphere or cell is formed.[17] Because of the gastroprotective property of phosphatidylcholine, the phytosome technology creates a small cell that protects the plant extract or active constituent from degradation by gastric secretions and gut bacteria.

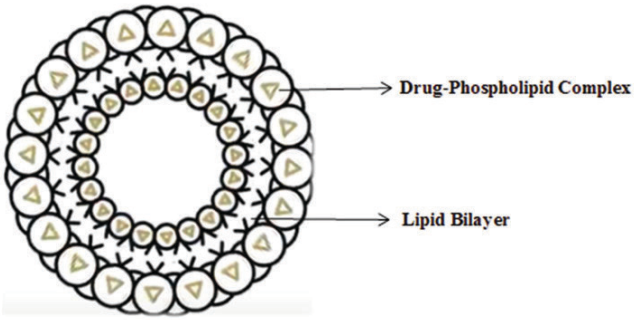

Figure 1: The basic structure of a Phytosome.

ANALYSIS OF PHYTOSOMES

Phytosomes are subjected to a variety of instrumental, *in vitro*, and *in vivo* tests. Scanning Electron Microscopy (SEM) may be used to classify these complexes.[18] It confirms the spherical shape of the phytosomes and indicates no impurity on the surface. Transmission Electron Microscopy (TEM) investigates the enclosed elements where the drug is entangled and its distribution inside the phospholipid mesh. Proton-Nuclear Magnetic Resonance (^{1}H-NMR) spectroscopy is used to calculate the formation of the complex between the active constituent and the lipid fragment.[19] Carbon-Nuclear Magnetic Resonance (^{13}C-NMR) spectroscopy records all the carbons of phytoconstituents.[20] Fourier-Transformed Infrared (FT-IR) spectroscopy helps to understand the resulting complex.[21] Ultraviolet-Visible (UV-Vis) spectroscopy is used to establish a chemical spectral signature of phospholipid complexes.[22] Differential Scanning Calorimetry (DSC) and X-Ray Diffraction (XRD) are used to determine the melting

point of the phytoconstituents, which is crystal in nature.[23] For pharmacokinetic studies of phytochemicals, liquid chromatography/atmospheric pressure chemical ionization mass spectrometry (LC/APCI-ITMS) has proven to be a very useful method.[24] Infrared-Photo-Pulse-Plethysmography, Laser Doppler Flowmetry, High-Performance Contact Thermography, Computerized Videothermography, and Optic Probe Videocapillaroscopy were used to investigate the impact of Phytosome type on the vasomotor function and skin microcirculation of the lips, hands, arms, and female breast in human subjects.[25]

MECHANISM OF FORMATION

Phosphatidylcholine is a bifunctional agent with a lipophilic phosphatidyl moiety and a hydrophilic choline moiety in nature. The phosphatidylcholine molecule's choline head binds to these compounds, while the lipid-soluble phosphatidyl part, which includes the body and tail, envelopes the choline-bound content. As a result, phytoconstituents form a lipid-compatible molecular complex with phospholipids known as the phyto-phospholipid complex.[26]

PREPARATION PROCEDURES AND STEPS

Phytosomes are novel complexes made by reacting two to three moles of a natural or synthetic phospholipid, such as phosphatidylcholine, phosphatidylethanolamine, or phosphatidylserine, with one mole of a component, such as flavor-lignanans, in an aprotic solvent such as dioxane or acetone, from which the complex can be isolated.[27] The ratio of these two moieties in the dynamic development of phytosomes ranges from 0.5 to 2.0 moles (**Figure 2**). A 1:1 ratio of phospholipids to flavonoids is the best. In phytosome preparations, phospholipids are chosen from a category that includes soy lecithin, phosphatidylcholine, phosphatidylethanolamine, and phosphatidylserine, all of which have the same or separate acyl group and are mainly extracted from palmitic, stearic, oleic, and linoleic acid.[28] Few liposomal drug complexes work in the presence of water or a buffer solution, while phytosomes work with a lower dielectric constant solvent. In chloroform, ethyl ether, or benzene, starting materials like flavonoids are insoluble. Since developing phytosomes, they become highly soluble in these solvents. The existence of a true stable complex is responsible for the transition of chemical and physical properties.[29]

ADVANTAGES OF PHYTOSOMES

Phytosomes improve the oral and topical absorption of lipid insoluble polar phytoconstituents, resulting in higher bioavailability and hence a greater clinical value. If the absorption of active constituent(s) improves, so does the dosage demand. Phosphatidylcholine, which is included in the processing of phytosomes, is a hepatoprotective as well as a transporter, resulting in a synergistic impact when hepatoprotective compounds are used. Since phosphatidylcholine molecules and phytoconstituents shape chemical bonds, phytosomes have a higher stability profile.[30]

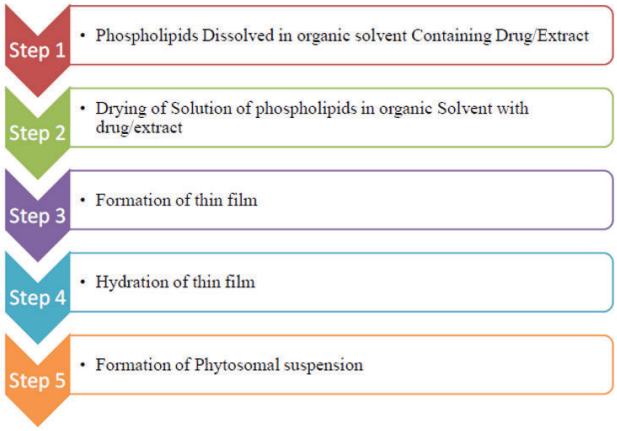

Figure 2: Basic steps for the formation of Phytosomes.

PROPERTIES OF PHYTOSOMES

Chemical properties

Phytosomes are a mixture of a natural commodity and naturally occurring phospholipids, such as soy phospholipids. In a suitable solvent, stoichiometric quantities of phospholipid and substrate are combined to form a matrix. The major phospholipid-substrate association is due to the forming of hydrogen bonds between the polar head of phospholipids (*i.e.* phosphate and ammonium groups) and the polar functionalities of the substrate, according to spectroscopic results.[31] Phytosomes take on a micellar appearance when exposed to water, creating liposomal-like structures. In liposomes, the active principle is dissolved in the internal pocket or floating in the layered membrane, while in phytosomes, the active principle is anchored to the polar head of phospholipids, being an integral part of the membrane, as in the case of the catechindistearoyl phosphatidylcholine complex, where H-bonds are formed between the phenolic hydroxyls of the catechindistearoyl phosphatidylcholine complex.[32]

Biological properties

Phytosomes are advanced herbal derivatives that are more easily consumed, utilized, and therefore yield greater outcomes than traditional herbal extracts. Pharmacokinetics and pharmacodynamic experiments in laboratory organisms and human subjects have shown that the phytosome has a higher bioavailability than non-complexed botanical variants.[33]

DIFFERENCE BETWEEN PHYTOSOME AND LIPOSOME

A liposome is produced by combining a water-soluble material with phosphatidylcholine in a certain ratio under specific conditions, similar to phytosomes. The phosphatidylcholine molecules cover the water-soluble material, forming no chemical bond. The water-soluble compound can be surrounded by hundreds or even thousands of phosphatidylcholine molecules.[34] In the phytosome phase, however, the phosphatidylcholine and plant components actually shape a 1:1 or 2:1 molecular complex, containing chemical bonds, depending on the substance(s) complexes (**Figure 3**). Because of this discrepancy, phytosomes are far more consumed than liposomes, resulting in higher bioavailability. In topical and skincare materials, phytosomes are superior to liposomes.[35]

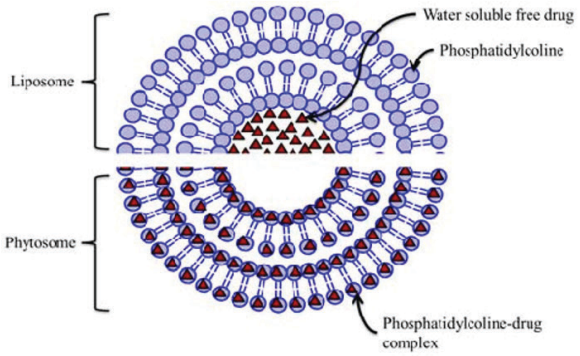

Figure 3: The basic difference between phytosomes and liposomes.

COMMERCIAL PHYTOSOMES PRODUCTS

Pharmacokinetics and pharmacodynamic experiments in laboratory organisms and human subjects have shown that the phytosome has a higher bioavailability than non-complexed botanical variants. Related things have been investigated with several commercially available goods.[36]

- **LEUCOSELECT®:** It's made up of oligomeric polyphenols (grape procyanidins) that have been combined with soy phospholipids. Procyanidins, which are commonly known to have a protective impact on the cardiovascular system across an interconnected network of complex mechanisms of action, including a distinct antioxidant effect, have significantly increased oral bioavailability as a result of this. It's made up of phospholipid-coated oligomeric polyphenols (grape procyanidins) of different molecular sizes. The procyanidins flavonoids' significantly enhanced oral bioavailability provides significant security for the cardiovascular system and other organs across a network of pathways that go beyond their high antioxidant potency.
- **GINKGOSELECT®:** It's a generic extract of *Ginkgo biloba* leaves in an easily absorbable shape. The primary signs are cerebral insufficiency and peripheral vascular diseases, and it is useful assistance in cases where cerebral performance is impaired. Its improved oral bioavailability and tolerability render it an excellent option for long-term care. It's a generic extract of *Ginkgo biloba* leaves that's more easily absorbed. Cerebral insufficiency and peripheral vascular diseases are the most common indications, and they may also help with impaired cerebral circulation. Because of its enhanced oral bioavailability and tolerability, it is the best Ginkgo product for long-term use.
- **GREENSELECT®:** It comprises a fully uniform polyphenolic fraction (no less than 66.5 percent) derived from green tea leaves, which is primarily described by the inclusion of epigallocatechin and derivatives. These compounds are effective in vitro modulators of a variety of biochemical processes implicated in the pathogenesis of significant chronic degenerative diseases including cancer and atherosclerosis. Green tea polyphenols' oral bioavailability is greatly improved as they are complexed with phospholipids. It is made up of a fully uniform polyphenolic fraction (no less than 66.5 percent) derived from green tea leaves, with epigallocatechin and its variants being the most prominent. These compounds are effective modulators of several biochemical processes related to the collapse of homeostasis in diseases including cancer and atherosclerosis. Green tea polyphenols' low oral bioavailability is greatly improved when they are complexed with phospholipids.
- **SILIPHOS®:** It protects the liver from a variety of causes. It is the most absorbable source of silybin identified to date, allowing it to penetrate the target organ, the liver, at concentrations that are anti-hepatotoxic.
- **MIRTOSELECT®:** It contains bilberry extract, which produces anthocyanosides. These are potent antioxidants that increase capillary tone, decrease abnormal blood vessel permeability, and boost capillary tone. They have a lot of promise in terms of treating retinal blood flow complications and venous insufficiency.
- **SABALSELECT®:** It contains a saw palmetto berry extract obtained by supercritical CO_2 (carbon dioxide) extraction. It contains fatty acids, alcohols, and sterols, both of which are beneficial to prostate health. This extract can help non-cancerous prostate enlargement in particular.
- **LYMPHASELECT™:** It contains a *Melilotus officinalis* uniform extract. This medication is used to treat venous diseases, such as persistent venous insufficiency in the lower limbs.
- **OLEASELECT™:** It is a more recent preparation made from polyphenols found in olive oil. These are active free radical scavengers (antioxidants) that of-

ten have anti-inflammatory properties and prevent the dangerous oxidation of LDL cholesterol.

- **POLINACEA™:***Echinacea Angustifolia* is used to make this immunomodulating preparation. It contains echinacoside and a high-molecular-weight polysaccharide that is unusual. This supplement improves immune function in the face of a toxic threat. The phytosome technology allows cost-effective distribution and synergistic effects from the phospholipid nutraceuticals found in nature for any of these groundbreaking phytomedicines.

HERBAL CONSTITUENTS USED IN PHYTOSOMAL DRUG DELIVERY

Flavonoids

Plants contain a variety of health-promoting compounds, the most notable of which are flavonoids. Flavonoids are used in a broad range of foods and medicinal plants and were first discovered for their antioxidant effects. More than 4,000 naturally occurring flavonoids have been described to date, each with its molecular structure and three-dimensional form.[37] Polyphenols are a wider category of dietary antioxidants that include flavonoids (literally, having more than one phenolic ring). The triple ring complexes of flavonoids distinguish them. Flavonoids are divided into subclasses based on the degree of oxidation of the oxygen heterocycle or C-ring. Flavonoid biology is concerned with the 3-D shape or "configuration" of molecules.[38] Flavonoids have been discovered to defend weak molecular sites on cells, as well as to stimulate or suppress active sites. The flavonoid molecule is PC attached to the device phytosome. Flavonoids are used at the highest concentrations in berries and other seeds, a few herbs, and cocoa and tea drinks. Flavonoids are generally poorly ingested from food; the difference occurs where more than 10% of the administered dosage reaches the bloodstream.[39] Epidemiological data indicate that reduced flavonoid consumption is linked to a higher incidence of cardiovascular disease, although the evidence isn't definitive. Flavonoids downregulate receptors for prostaglandins, cytokines, or hormones on cancerous or other dysfunctional cells are a hot topic in current research. In the anti-inflammatory, anti-allergic, antiviral, anticancer, and immunostimulant applications of flavonoids, molecular structure can be just as essential as antioxidant action.[40] Indena scientists then achieved a milestone in phytomedicine by converting flavonoid preparations with the highest health-giving ability into phytosomal preparations.[41]

Terpenoids

Isoprene units are used to make natural materials and associated chemicals. They incorporate oxygen in several different functional classes. In the same way, as terpenes are separated by the number of carbon atoms, this class is divided by the number of carbon atoms. The loss or change of a fragment, usually a methyl group, may cause terpenoid skeletons to vary from strict additivity of isoprene units.[42]

Carotenoids

Carotenes, xanthophylls, and other substances that result from skeleton rearrangement or partial skeleton failure fall under this category. Retinoids are not allowed.[43]

Isoprenoids

Compounds extracted from isoprene (2-methyl-buta-1,3-diene), whose skeleton can be seen infrequent occurrences in the molecule. By losing or shifting a fragment, most usually a methyl group, the skeleton of isoprenoids may vary from strict additivity of isoprene units. Both hydrocarbon and oxygenated derivatives are included in this category.[44]

Terpenes

Hydrocarbons with carbon skeletons resulting from isoprene [CH_2=C(CH_3)CH=CH_2] of biological heritage. C_5 hemiterpenes, C_{10} monoterpenes, C_{15} sesquiterpenes, C_{20} diterpenes, C_{25} sesterterpenes, C_{30} triterpenes, C_{40} tetraterpenes (carotenoids), and C_5n polyterpenes are subdivided into this grouping.[45] Phospholipids from soy, mostly phosphatidylcholine, are lipid-phase compounds that have been successfully used to render flavonoids lipid compliant. Phosphytidyl choline is miscible in both the water and oil/lipid stages, and when swallowed by mouth, it is well absorbed.[46] The molecular properties that fit PC for this function also make it close to ideal for its Phytosome role. Phosphytidyl choline is the primary molecular building block for cell membranes, and the molecular properties that suit PC for this role also make it close to ideal for its Phytosome role.[47]

CONCLUSION

Phytosomes are a form of advanced herbal extract that is easier to digest and yields better results than standard herbal extract. Phytosomes have strengthened pharmacokinetic and pharmacological parameters, enabling them to be used to manage a wide range of illnesses. Phytosome absorption is slightly greater in the gastrointestinal tract than in the human component, resulting in a higher plasma level. After rigorous screening and collection of phytoconstituents for pharmaceutical usage, phytosomal drug delivery may be tailored for treating various diseases such as cancer, cardiovascular disorders, and inflammation.

Conflict of Interest

The author declares no conflict of interest.

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Author's Contribution

Author did the literature survey from standard databases, collected all essential elements, and wrote this manuscript.

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