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REVIEW ARTICLE

Recent Advancements and Applications of Phospholipid Complexes: A Strategy to Enhancing the Bioavailability of Phytopharmaceuticals

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Abstract: Phytopharmaceuticals are herbal medicines that include standardized extracts, bioactive fractions, and purified phytoconstituents. They have been used for the cure, treatment, and mitigation of diseases since ancient times. Phytopharmaceuticals have a wide array of health benefits but their therapeutic efficacy is limited due to poor absorption, low bioavailability, and early elimination profile. A novel phospholipid complex is a newly introduced patented technology initially developed to incorporate standardized plant extracts/fractions or water-soluble phytoconstituents into phospholipids to produce a lipid compatible molecular complex, called phytosome, which improves their absorption and bioavailability. In herbal formulations, phytosome is the most advanced dosage form that has upgraded absorption rate and improved pharmacokinetics in comparison with conventional products. Phospholipid-complex is the result of hydrogen bonding between phospholipids and phytoconstituents, which offers maximum incorporation of herbal active ingredients into the lipidic layer and core. The increased therapeutic efficacy is due to the formation of amphiphilic phospholipid complex of herbal medicine. This review highlights the role of phospholipids in the delivery of herbal bioactives and natural extracts with special emphasis on phytosomes. Moreover, the current status of bioavailabilities, commercial products, patents, and clinical trials of phytosomal system of phytopharmaceuticals were addressed.

Keywords: Phospholipid-complex, phytopharmaceuticals, bioavailability, phytosomes, clinical trials, herbal medicines.

1. INTRODUCTION

Phytopharmaceuticals are herbal preparations whose efficacy rests on one or numerous plant substances or active ingredients present therein. The terms *phyto-pharmakon* / phyto-pharmaceuticals are resultant of the Greek descriptions *phyton* which means plant and *pharmakon* meant for medicine. These herbal preparations are made up of different plant parts like bark, flowers, leave, blossoms, herbs, or roots. In contrast to modern medicine, herbal medicines can act on various targets (receptors, enzymes, hormones, *etc*.) for eliciting pharmacological activities as they have diverse kinds of phytoconstituents [1]. Since age, herbs are being used as medicines for the treatment of various diseases. Most of the world's population depends on medicinal plants for their primary health care needs, and they are most widely used for the treatment of various acute and chronic diseases.

The nature of plant extracts is very complex as they constitute both polar and non-polar types of chemical constituents. Uses of botanicals as therapeutic agents are limited because they have low absorption due to poor physicochemical properties. Most of the biologically active constituents of medicinal plants are water-soluble like flavonoids, tannins, glycosidal aglycones, *etc*. are poorly absorbed either due to their large molecular size, which cannot be absorbed by passive diffusion, or due to their poor lipid solubility, thus severely limiting their ability to transport across lipid-rich biological membranes, resulting in their poor bioavailability. Therefore, they have poor pharmacokinetics in the human body and limit their therapeutic potency apart from their numerous health benefits [2]. The effectiveness of any medicine depends on the effective level of the drug delivery system. In this context, a novel phospholipid complex (phytosome) is pioneering among other delivery systems to overcome the shortcomings of phytopharmaceuticals [3]. Phospholipids have an amphiphilic character and biocompatibility profile and together with their self-organization properties in the water systems, they allow the production of supramolecular systems with high entrapment efficiency of both lipophilic and hydrophilic compounds. Additionally, these supramolecular systems improve the bioavailability of the encapsulated compounds and can be manipulated to obtain targeted delivery systems of desired size [4]. Moreover, phospholipid complex offers several advantages such as increased solubility, enhanced absorption/bioavailability, improved gastric stability, controlled release system, reduced

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dose-related adverse effects, less mutagenic and more biocompatibility. Novel phospholipid complex systems of phytopharmaceuticals have more bioavailability with improved therapeutic effects than a simple herbal extract due to its enhanced capacity to cross the lipid-rich biomembrane and reach blood circulation [5]. These systems have been successfully employed with different pharmaceuticals (gingko, bacopa, turmeric, milk thistle, cocoa, hypericum, andrographolide, gallic acid, mangiferin, chlorogenic acid, naringenin, resveratrol, quercetin, curcumin, hesperetin, ursolic acid, *etc*. for improving their therapeutic efficacy and bioavailability [6]. Phospholipids-based drug delivery system is being used for treating various disorders such as diabetes, hepatic problems, osteoporosis, memory loss, immune disorders, cancer, *etc*; as they are incompletely curable by today's modern medicine [7]. A recent study has demonstrated that by using phytosomes as drug delivery system helps to cure disease without side-effects.

2. FORMULATION ASPECTS OF PHOSPHOLIPID COMPLEX

All biological membranes consist of a mixture of different classes of phospholipids, such as phosphatidylcholine (PC), phosphatidylethanolamine (PE), phosphatidylinositol (PI), phosphatidic acid (PA) and phosphatidylserine (PS) [8]. Detailed structures of these phospholipids are given in Fig. (**1**).

Phosphatidylcholine (PC) is a phospholipid, which is a building block for cell membranes [9]. Phosphatidylcholine has an accessibility that can be used as a nutritive supplement. PC is compatible with various pharmaceuticals and other nutrients. It is completely bioavailable (around 90% of the administered amount is absorbed over more than 24 hours) and is a great emulsifier that has the ability to elevate the bioavailability of these supplements when Co-administered [10]. For potent drugs, phospholipid complex techniques are used to increase therapeutic efficiency. These serve as a better targeting agent to produce an effect at specific sites [11].

2.1. Types of Phospholipids

It is investigated that all phospholipids are not similar. They vary from each other in size, shape, and chemical structure. Therefore, they are categorized into various types depending on the type of chemical entity that is involved in the phosphate group. Therefore, simple organic molecules change the phosphate group [12, 13].

Following are the types of phospholipids.

2.1.1. Phosphatidylcholine (PC)

It is found in cell membranes and is the most abundant. In this, the phosphate group binds to choline. It is significant to sustain the structure of the cell membrane and found to be significant for the suitable efficiency of the liver, along with the absorption of lipids. These phospholipids are one of the constituents of the bile and benefit in fat digestion. Furthermore, it plays a significant role in the transportation of cholesterol and lipids to several organs [14].

2.1.2. Phosphatidylethanolamine (PE)

As suggested, an ethanolamine unit is involved in the phosphate group. Second-most rich type of phospholipid in the cell membrane. Its minor head style is relaxed for the proteins to be associated inside the membrane, therefore, making the membrane synthesis and budding process achievable. Furthermore, this constitutes a significant component of the mitochondrial membrane [14].

2.1.3. Phosphatidylserine (PS)

In this phospholipid, the phosphate group is attached to the amino acid serine, which is restricted to the innermost part of the cell membrane. These phospholipids are created to play a vital role in cell signaling processes. It is well known that the occurrence of this phospholipid on the surface of the external membrane of dying cells would signal the macrophages to digest them. In platelets, these phospholipids will aid in the clotting of blood [14].

2.1.4. Phosphatidylinositol (PI)

In this phospholipid, an inositol unit is attached to the phosphate group. These are observed in numerous types of cells and tissues and are particularly plentiful in brain cells. These are found to be substantial for the development of cell signaling molecules. These would also help in the binding of proteins and carbohydrate units to the outer cell membrane [14].

2.2. Methods of Phospholipid Complex Preparation

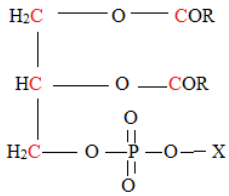
The following methods are used for the preparation of phospholipid complexes such as mechanical dispersion methods, salting out- anti solvent precipitation and solvent evaporation. Schematics of the basic preparation method of phytopharmaceutical incorporating phospholipid complex system are shown in Fig. (**2**) after preparing this basic, below mentioned methods are used further.

2.2.1. Solvent Evaporation

In this technique, phytoconstituents and Phosphatidylcholine are added to a flask that contains organic solvent. Then, the mixture containing the flask is heated for 1 hour at 40°C to achieve maximum entrapment of the drug when phytosomes are formed. The rotary evaporator is used to evaporate the organic solvents. 100 mesh sieves are used to sieve the thin film formed and are stored in desiccators overnight [15, 16]. To attain stability, an amber-colored bottle is used for storing the phytosomes, which are flushed at room temperature containing nitrogen gas [17].

2.2.2. Salting Out-anti Solvent Precipitation

In this technique, a flask is firstly filled with the desired amount of organic solvent, then after this phytoconstituent and phosphatidylcholine are added to the flask. The mixture is then placed on a magnetic stirrer. Then, the solution is intense and n-hexane (anti-solvent) is further added [18]. A precipitate is formed which is filtered under vacuum and kept in a sealed amber colored glass container.



Structure of Phospholipid

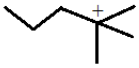
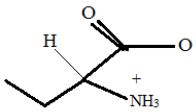
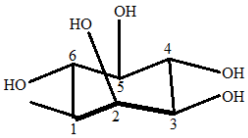
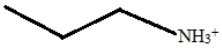
Phospholipids	X	Net charge in Ph 7	Phospholipid ratio	Route of administration
PA		-1	-	Topical
PC		0	-	Capsule
PS		-1	1:2	Topical
PI		-1	1:2	Topical
PE		0	1:7	Capsule

Fig. (1). Structure of different types of phospholipids.

Fig. (2). Formulation schematics of phospholipid complex of phytopharmaceuticals. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

2.2.3. Mechanical Dispersion

In this technique, the lipids are mixed in the organic dissolving agent and taken in interaction with a liquid phase comprising the drug [19]. Primarily phosphatidylcholine is mixed in diethyl ether, which is gradually injected into a liquid solution that requires to be encapsulated. The sequential removal of the organic solvent results in the development of Phytophospholipid complexes. Innovative approaches for complex formation include supercritical fluids (SCF), which embrace the gas antisolvent technique compressed antisolvent process (PCA) and supercritical antisolvent method (SAS) [20].

3. PHOSPHOLIPID-COMPLEX FOR DELIVERY OF HERBAL EXTRACTS AND HERBAL BIOACTIVES

Novel drug delivery systems have many essential advantages in comparison to conventional dosage forms. These systems provide better controlled delivery of drugs as they are non-toxic, biodegradable, and have the property of loading both hydrophilic as well as hydrophobic drug molecules. They sustain the drug release as they undergo controlled hydration. Application of novel drug delivery imparts smaller particle size in liquid crystal dispersion, nano particle dispersion vesicle micellar solutions up to 10-400 nm. Using novel techniques such as phospholipids shows extreme solubilization properties for lipophobic compounds, which shows a remarkable development in various delivery of botanical drugs. Through many clinical studies, it is determined that manydrugs have failed in trials just because of liver toxicity. The liver protecting property of phospholipids gives an advantage to the carrier drug delivery system. Various phytoconstituents which are extracted from different plant sources in the form of terpenoids, flavonoids, or carotenoids provide many different pharmacological actions such as free radical scavenging, hepatoprotective, anti-inflammatory, platelet antiaggregating, peripheral vasodilator and antioxidant. Therefore, due to the large problem of poor absorption, there are limitations for these active phytoconstituents. It has been analyzed that flavonoids show low absorption because they form complexation when coming in contact with gastric fluid and get degraded by different bacteria present in the body. The efficiency of all herbal products always depends on the active compound effectiveness level. For example, *milk thistle* delivers an actual level of silybin and the same as for panax ginseng in *ginsenosides*. According to various studies, it has been proved that all phytoconstituent activities have been enhanced successfully with the help of phytosomes and show better therapeutic effects when administered in the body (Tables **1** and **2**) [21].

Table 1. Phospholipid-complex of some herbal extracts and herbal bioactives.

S. No.	Phytosomes	Phytoconstituents and Herbal Source	Dose (mg)	Bioavailability	Characteristics	Indication	References
1.	*Ashwagandha phytosomes complex*	*Withanolides* from *withania somnifera*	100	C_{max}: 6.39 ± 0.11 mg/ml, F= 70-80%.	*Ashwagandha* has a bitter, astringent and sweet rasa, heating virya and a sweet vipaka	Antioxidant	Keerthi B, *et al.*
2.	*Ximenoil*	*Xemenynic acid, ethyl xemenynate* from *santalum album*	——	C_{max}: (0.112±0.008) mg·L-1, F= 80-90%.	*Ximenoil* is relaxing, soothing, cooling, sensual, and valued for its own sweet, warm, rich balsamic aroma.	Improves microcirculation	Kalita B, *et al.*
3.	*Adulsa capsules phytosomes*	Alkaloids, carbohydrate tannins, sterols, phenols from *adhatodavasica*	20	C_{max}: 0.92 ± 0.032 mg/ml, F= 80-85%.	Perennial shrub has leathery leaves	Respiratory disease	Shaikh N, *et al*. [6]
4.	*Quercetin–phospholipid complex*	Flavonoids from onions, grapes, berries, cherry, broccoli, and citrus fruits	10-20	-	-	Antioxidant, anti-inflammatory, anti-allergic and antitoxic effects	Maiti K, *et al.*
5.	*Hesperetin phospholipid complex*	Flavanones from *hesperetin 7-rhammnoglucoside*	100	C_{max}: 825.787410.63 ng/ml, F= 40-60%.	It has a bitter taste found in citrus fruits,	Antioxidant, hemorrhoids, varicose veins	Maiti K, *et al.*
6.	*Ellagic acid phospholipid complex*	*Ellagitannin*s from dimeric derivative of *gallic acid*	25	C_{max}: 213 ng/ml, F= 40-50%.	It has a bitter taste found in strawberries, cranberries, *etc*.	Antioxidant, antimutagenic, anti-inflammatory, and cardioprotective activities	Murugan V, *et al.*
7.	*Phospholipid Complex of andrographolide*	*Andrographolide* from *Andrographis paniculata*	25-50	C_{max}: 393 ng/ml, F= 30-50%.	It is bitter and is the source of several diterpenoids which are bitter water-soluble lactone.	Hepatoprotective activity	Maiti K, *et al.*

(Table 1) contd…

S. No.	Phytosomes	Phytoconstituents and Herbal Source	Dose (mg)	Bioavailability	Characteristics	Indication	Reference
8.	*Resveratrol complex with hydrogenated soy phosphatidyl choline*	*Resveratrol* from grapes juice, peanuts, coca.	4-8	C_{max}: 573 ng/ml, F= 40-50%.	It is found in fruits, plants, and red wine and bitter taste	Cardio protective	Mukherjee K, *et al*. [11]
9.	*Palmetto berries phytosomes*	Fatty acids, alcohols and sterols	320	-	-	Non-cancerous prostate enlargement, antioxidant	Acharya N.K, *et al*.
10.	*Bilberry phytosomes*	*Anthocyanosides* extract	173	C_{max}: 2-3 µg/ml., F= 50-55%.	Dark blue berries which have a sweet taste.	Antioxidants, improvement of capillary tone	Acharya N.K, *et al*.
11.	*Mangiferin phospholipid complex*	*Xanthonoid* from *mangiferaindica*	30 & 60	C_{max}: 44.16 µg/mL, F= 70-75%.	Sour in taste found in mango.	Antioxidant, hepatoprotective	Bhattacharyya S, *et al*.
12.	*Gallic acid–phospholipid complex*	Polyphenol present in strawberries, amla, pineapples, tea leaves, Red and white wines, bananas, witch hazel, gallnuts, oak bark, sumac & peels of apple	150	C_{max}: 0.22 micromol/L, F= 60-70%.	It has a bitter taste found in strawberries, gallnuts, *etc*.	Hepatoprotective activity	Bhattacharyya S. *et al*.
13.	*Ferulic acid–Phospholipid complex*	*Ubiquitous* natural phenolic from wheat, rice, barley, oats, citrus fruits, and tomatoes	1	C_{max}: 8174.55 ng/L, F= 70-75%.	It is found in a number of vegetable sources, particularly in popcorn and bamboo shoots.	Melanogenesis inhibition	Li Li, *et al*.
14.	*Luteolin–phospholipid complex*	Flavonoid from celery, thyme, green peppers, and chamomile tea	2000	C_{max}: 174.55 ng/L, F= 60-75%.	-	Antioxidant, anti-inflammatory, cardiovascular protection and anti-cancer effects	Sabzichi M, *et al*. Junaid Khan, *et al*. 2011 [37]
15.	*Abutilon indicum, piper longumphytosomes*	Quercetin, glycosides, alkaloids, terpenoids, Flavonoids, steroids, *geraniol*, saponins, sesquiterpenes, lactones, phenolic compound, *β-setosterol gallic acid* and caryophyllene from leaves of a *indicum* (*malvaceae*) and *p. longum (piperaceae)* fruit	5000	-	-	Hepatoprotective	Sonam M. *et al*.
16.	*Rutin-loaded nanophytosomes*	Bioflavonoids	___	-	-	Antioxidant	Hooresfand Z, *et al*.
17.	*Phyllanthus emblica extract phospholipid complex*	Polyphenols from *phyllanthusemblica* fruit extract	1000	C_{max}: 84.55 ng/L, F= 80-85%.	-	Photoprotectant, oxidative stress	Pereira A, *et al*.
18.	*Rosmarinic acid–phospholipid complex*	Polyphenol from mint	20	C_{max}: 215.29 ng/mL, F=0.91% to 1.69%.	It is found in hornworts, and has a sour taste.	Cancer and atherosclerosis, anti-inflammatory, anti-allergic	Yang J.H, *et al*.
19.	*Pomegranate extract-phospholipid*	*Anomeric ellagitannins* from *punicagranatum*	___	-	-	Alzheimer's disease protection, antioxidants, digestion, vitamin C, cancer prevention, heart disease, arthritis, anti-inflammatory	Vora A.K, *et al*.
20.	*Ursolic acid-phospholipid complex*	*3β-hydroxy-urs-12-en-28-oic-acid* from apple peel and many plants	10-20	-	-	Hepatoprotective activity	Sayan Biswas, *et al*. 2019

Table 2. Phospholipids-complex based some commercial products of herbal extract and bioactive.

S. No.	Phytosome	Doses (mg)	Phytoconstituents Complex with Phosphatidylcholine	Indication	References
1	*Mirtoselect*	160-320	*Anthocyanoside* from *vaccinum Myrtellus*	Antioxidant, anti-inflammatory, diabetic retinopathy	SuryawanshiJ.A.S.2011
2	*Silymarin*	-	*Silymarin* from seeds of *milk thistle*	Antihepatotoxic	SuryawanshiJ.A.S.2011
3	*Silybin*	120	*Silybin* from *Silybum marianum*	Antioxidant for skin, hepatoprotective, food product	SuryawanshiJ.A.S.2011
4	*Lymphoselect*	6-20	Melilotoside, terpenoids from *melilotus officinalis*	Anti-inflammatory, thromboflabitis, antiedema	Maryana W. *et al*. 2015
5	*Ginkgo*	120	*24% ginkgo flavonglycosides* from *ginkgo biloba*	Antiageing agent, vascular lining, protects the brain	Maryana W. *et al*. 2015
6	*Zanthalene*	-	*Zanthalene* from zanthoxylum	Soothing, anti-itching, anti-irritant, bungeanum	Maryana W. *et al*. 2015
7	*Ginseng*	150	Ginsenoside 37.5% from *panax ginseng*	Immunomodulator, neutraceutical, food product	Maryana W. *et al*. 2015
8	*Olive oil/Oleaselect*	_	Polyphenols, verbacoside, tyrosol, hydroxytyrosol from oleaeuropoeasp.	Antioxidant, anti-inflammatory, antihyperlipidemic	Kalita B, *et al*. 2013
9	*Green tea*	50 to100	*Epigallocatechin3-O-gallate* from *Camelia sinesis*	Anticancer, neutraceutical and systemic antioxidant	Kalita B, *et al*. 2013
10	*Milk thistle*	150	Flavonoids from *silymarin*	Liver protectant	Kalita B, *et al*. 2013
11	*Grape seed*	50 to100	*Procyanidine* from *vitis vinifera*	Systemic antioxidant, neutraceutical, cardioprotective	Kalita B, *et al*. 2013
12	*Crataegus*	_	*Vitexin-2"-o- rhamnoside* from *hawthorne flower*	Antioxidant	Kalita B, *et al*. 2013
13	*Hawthorn*	100	Flavonoids from *crataegus sp*.	Hypertension, food products and other heart diseases	Ljiljana Djekic, *et al*. 2019
14	*Escin β-sitosterol*	3% gel	*Escin ß-sitosterol* from horse chestnut fruit	Anti-oedema, vasoactive properties	Ljiljana Djekic, *et al*. 2019
15	*Centella*	60-120	Terpenes from leaves of *centellaasiatica leaf*	Antiulcer, anti-hair loss, wound healing, vein, and skin disorders.	Arijit Gandhi, *et al*. 2012 [34]
16	*Sericoside*	-	*Sericoside* from terminalia sericea bark root	Anti-wrinkles	Arijit Gandhi, *et al*. 2012 [34]
17	*Echinacea*	400	*Echinacosides* from *echinacea Angustifolia*	Immunomodulator, neutraceutical	Arijit Gandhi, *et al*. 2012 [34]
18	*Sabalselect*	320	Phytosterol from *serenoarepens (bartr)*	Non-cancerous prostate enlargement.	Arijit Gandhi, *et al*. 2012 [34]
19	*Curcumin*	250	*Curcumin* from *curcuma longa*	Anti-inflammatory, antioxidant	Arijit Gandhi, *et al*. 2012 [34]
20	*Naringenin*	100 mg/kg	*Naringenin* from citrus Aurentium	Anti-oxidant	Arun K, *et al*. 2017
21	*18 ß-Glycyrrhetinic acid*	_	*18 ß-glycyrrhetinic acid* from *glycerrhyzaglabra / licorice rhizome*	Anti-inflammatory, soothing	Anil Kumar Sah, *et al*. 2017
22	*Swertia*	-	*Xenthones 26* from *swertia alternifolia*	Anti-oxidant	Anil Kumar Sah, *et al*. 2017
23	*Ginkgo biloba terpenes*	120	Bilobalide and ginkgolides from *ginkgo biloba leaf*	Soothing property	Jagruti Patel, *et al*. 2009 [35]
24	*PA2*	_	*Proanthocyanidin A2* from horse chestnut bark	UV protectant, anti-wrinkles	Jagruti Patel, *et al*. 2009 [35]
25	*Visnadex*		*Visnadin* from *amnivisnaga umbel*	Vasokinetic	Jagruti Patel, *et al*. 2009 [35]
26	*Ginkgo biloba dimeric flavonoids*	_	Dimeric flavonoids from *ginkgo biloba leaf*	Vasokinetic, lipolytic	Jagruti Patel, *et al*. 2009
27	*Virtiva*	-	Bilobalide, ginkgolides, ginkgo flavonglycosides from *ginkgo biloba* leaf	Vasokinetic	Jagruti Patel, *et al*. 2009 [35]

Water-soluble phytoconstituent changes to lipid-compatible molecular complexes called Phytosomes [22]. Phytosomes or phytolipid delivery system or planterosomes or herbosomesare ingenious lipid carriers [23, 24]. An innovation in these is developed by Indena Abdelkader [25]. Phytosomes presented great pharmacokinetic and pharmacodynamics activities than normal natural extracts [26] "Phyto" means plant while "some" means cell-like [27]. Phytosomes are readily bioavailable with respect to traditional herbal extracts to upgrade them to cross the membrane to reach systemic circulation [28]. The phytosomes create cells, which have a better ability to travel from a hydrophilic domain to the lipophilic domain of the enterocyte cell membrane and from that to the blood. In this way, it confirms that the drug is safely delivered by wiping out digestive secretion and gut bacteria [29]. The botanical extract is merged into phosphatidylcholine which is extracted from soy to produce complexation which is a further known as phytosome [30, 31] Sindhumol *et al*. represented Phytosomes diagrammatically in Fig. (**3**) where they stated that Phytosomes consist of hydrophilic group in which head is shown in yellow color and hydrophilic group is shown by blue color.

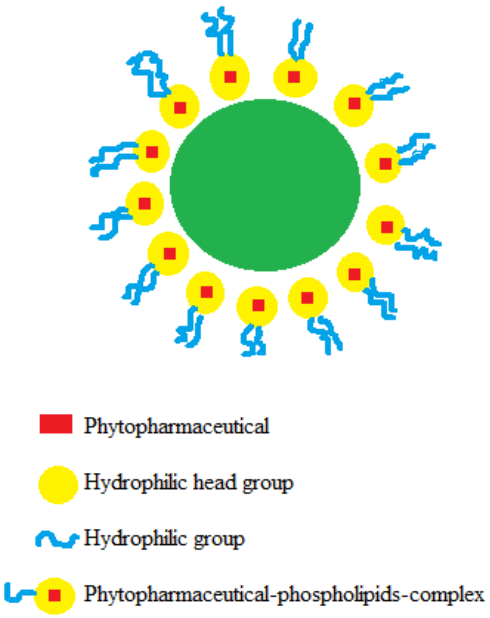


Fig. (3). Diagram of phytosomes. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Phytosomal formulation offer various characteristics including sustained release or prolonged action of phytomolecules, helping in solubilizing poorly soluble compounds, protecting from presystemic metabolism of drug molecules, maintaining the integrity of unstable compounds in gastric environment, providing all benefits of bioactive molecule at a reduced dose level, reduced side effects of active ingredients, enhancing bioavailability and producing better effects than their parent molecules Kumar *et al*. revealed in their article the sustained release activity of phytosomes.

Merits of phytosomes are as follows:

- Phytosomes increase the bioavailability and absorption of herbaceous extracts from the intestinal tract by forming phospholipid complexation.
- To increase the absorption of non-lipophilic herbal extracts from the intestinal lumen [32].
- Phytosomes impart the delivery of flavonoids for liver protection.
- Used to deliver liver-protecting flavonoids [33].
- Liver ailment treatment by enhancing the solubility of bile.
- It is hepatoprotective, so it provides a synergistic effect for the protection of the liver.
- It provides economical delivery of phytoconstituents [34].
- Used to enhance permeation of drugs through the skin for transdermal and dermal delivery.
- During the formulation preparation, drug entrapment occurs.
- It is also used in the delivery of protein, and peptide molecules.
- The vesicular system can act as non-invasive, passive, and available for commercial use.
- The combination is safe and approved for both cosmeceutical and pharmaceutical purposes.

4. PATENT ON PHYTOCONSTITUENTS BASED PHOSPHOLIPIDS-COMPLEX

A patent is a type of intellectual property that provides its owner the legal right to reject others from creation, application, trading, and importing any invention for a limited period of years, in exchange for reproducing an empowering public disclosure of the invention. Phytoconstituents are chemical compounds that occur naturally in plants. The patent is also given to phytoconstituents. Phytoconstituent patent is a grant given by a state to an inventor or to his assignee, providing exclusive rights to create, apply, exercise, and vend the invention for a limited period, in exchange for revelation in a patent specification. Various patents on phytoconstituents are filed for cosmetics (Table **3**).

5. CLINICAL TRIALS WITH PHOSPHOLIPID COMPLEX OR PHYTOSOME

In vitro and *in vivo* studies were conducted on developing phytosomes throughout the world for establishing their several health benefits. The clinical existence of phytopharmaceutical based phospholipid complex systems is the need of the day. Phytosome based clinical trials of various herbal extracts and herbal bioactives on certain health problems produced some interesting outcomes. Recent status on the clinical trials of phytoconstituents or extracts-based phytosomes is available on the website (clinicaltrials.gov) of U.S. National Institutes of Health (NIH). Different phases of clin-

Table 3. List of patents on phytoconstituent based phospholipids complex.

S. No.	Title	Applicant	Publication No. & Date
1.	Composition for prevention or treatment of skin inflammation comprising *Centella asiatica phytosome* and *Mori Radicis Cortex extract*	박목순, 김학성 Mok-soon Park, Hakseong Kim	KR102073009B1 & 2020-02-04
2.	Phytosome comprising *Centella asiatica* extracts and the method preparing thereof	충북대학교 산학협력단 Chungbuk National University Industry-University Cooperation Foundation	KR20190081126A & 2019-07-09
3.	Self-microemulsion composition of *breviscapine phytosome* and preparation method of composition	Chen Xiaoxin Long Chaofeng Xie, Chengshi Wu Xiong Liao Xiaoying Zhou Xiaoli Yuan Su	CN103110578B & 2014-11-12
4.	Compositions containing a *phospholipid-curcumin complex* and *piperine* as chemo sensitizing agent	Velleja Research Srl	EP2228062A1 & 2010-09-15 & EP2228062B1 & 2017-07-26
5	Formulation in an oily medium based on a *phosphatidylcholine-silybin* complex in phytosome and soft gelatin capsules prepared with such formulation.	Italmex S A	MX2017003184A & 2018-09-10
6.	*Proanthocyanidin B2* phospholipid compound, and preparation method and application thereof	Zhejiang Xiaoshan Hospital	CN102688501A & 2012-09-26
7.	Compositions for the treatment and prevention of vertigo and tinnitus including citicoline, *ginkgo biloba* extract and dimeric flavones of *ginkgo biloba*	Siit Srl Servizio Internazionale Imballaggi Termosaldanti	EP2018868A1 & 2009-01-28
8.	Aqueous dispersion of *camptothecin analogue-phospholipid complex* and method for preparing same	Shenyang Pharmaceutical University	CN101721364B & 2014-05-21 CN101721364A & 2010-06-09
9.	Phospholipid complexes of *olive fruits* or leaves extracts have improved bioavailability	Indana Espia	KR101548126B1 & 2015-08-28
10.	Method of producing a nanoscale phytosome system	Federal State Autonomous Educational Institution of Higher Education “Peoples’ Friendship University of Russia” (RUDN)	RU2680809C2 & 2019-02-27
11.	*Saussurea involucrate* extractive phytosome, oral cavity disintegrating tablet, and preparation methods of two	Xinjiang Uygur Autonomous Region Institute of Medicine	CN104383547B & 2017-11-14
12.	Preparation method and application of phospholipid complex with anti-oxidative stress	Shi Dongyun, Liu Shanlin, Xie Feizhou	CN103120798A & 2013-05-29
13.	Concentrated therapeutic phospholipid compositions	Acasti Pharma Inc	CA2779162C & 2018-02-06
14.	Target vector / phospholipid conjugate	Bracco, Swiss, Society, Anonymous	JP5735993B2 & 2015-06-17

Note: [35-38].

ical investigations have been performed, some of them have been completed, and some are active or recruited for different health problems. Details of phytosome-based clinical trials were represented in Table **4**.

6. CHALLENGES AND FUTURE PERSPECTIVES OF PHOSPHOLIPID COMPLEXATION TECHNIQUES

The method of incorporating these herbal drug extracts and molecules with healthy nutritive phospholipids has been developed as a key tool to develop pharmacokinetic and pharmacodynamic profiles of highly potent therapeutic phytoconstituents having poor bioavailability. The phyto-phospholipid complex has been researched and developed for a novel drug delivery carry system for providing systemic action, which was earlier originally designed for cosmetic use. Although this field of phytopharmaceuticals is considered, a broad spectrum of research needs to be expanded to address a variety of strategies for clinical advantage, stability, and preparation of drug delivery systems. Dichloromethane and tetrahydrofuran were basically used for the development of phyto-phospholipid complexes, which have been replaced by various solvents such as ethanol. These new solvent system for developing phyto-phospholipids imparts high efficiency for clinical applications. Traditionally, the solvent evaporation technique is widely used for the formulation and development of phyto-phospholipids. Therefore, the quality of various parameters like morphology, particle size, and hygroscopicity are based on the selections of suitable drying technique for residue and due to different

Table 4. Phospholipid-complex (phytosome) based clinical trials for health benefits and treatment of certain diseases (https://clinicaltrials.gov/).

S. No.	Phase	Trial	Status	Conditions	Interventions	NCT Number
1	Not Applicable	*Anthocyanin extract* and *phospholipid curcumin* in colorectal adenoma	Active, not recruiting	Colorectal adenoma Risk reduction	Dietary supplement: Mirtoselect® + Meriva® Dietary supplement: Placebo	NCT01948661
2	Phase III	*Silybin - Vitamin E- phospholipids complex* reduces liver fibrosis in patients with chronic hepatitis C treated with Peg-IFN-a and RBV	Completed	Liver fibrosis	Drug: Silybin 94 mg + phospholipids 194 mg complex + vitamin E 90 mg Drug: Placebo	NCT01935817
3	Phase II	A phase II study to assess the efficacy of combined treatment with *erlotinib* (Tarceva) and *silybin phytosome* (Siliphos) in patients with EGFR mutant lung adenocarcinoma	Unknown	Carcinoma, non-small cell lung	Drug: Erlotinib Dietary supplement: Silybin-phytosome	NCT02146118
4	Phase IV	Effects of *Greenselect phytosome*® on weight maintenance after weight loss in obese women	Completed	Obesity	Dietary supplement: Globes® Dietary supplement: Placebo	NCT02542449
5	Phase II	The effect of high-dose *silybin phytosome* in men with prostate cancer	Completed	Prostate cancer	Drug: Silibin-phytosome	NCT00487721

processing steps, it is considered a time taking technique. To overcome the traditional difficulties such as the size of particles or molecules and distribution of particles are often managed by the supercritical fluid technique under various mild conditions of temperature. It is also considered that the uniformity and consistency of molecule or particle size have impacted the enhancement of systemic bioavailability. According to the traditional techniques, the research works are mostly considering the ratio of 1:1 for drug and phospholipid, respectively. Moreover, it has been studied that the ratio different from 1:1 has produced better pharmacological and physiological actions. The phyto-phospholipid complex yield in various investigations is analysed from about 25% to over 90% and has been credited to various formulation factors like API to phospholipid proportion, temperature and duration of preparation that has appeared to influence the yield of the carrier system. Therefore, in future research work or practice, this characteristic has to be considered for the formulation aspects. Many advanced tools and technologies which are stated as spherical symmetric designing tool, factorial design and others are used for the research purpose to upgrade the molar ratios of drug applicants with phospholipids alongside their temperature and different factors to achieve enhanced drug release profile and entrapment efficiency. The relation between pharmacokinetics parameters stated that the drug pharmacological efficacy of phyto-phospholipids is inadequate. Phyto-phospholipid complex evaluation and characterization have given importance without undergoing clinical trials when considered for pharmacokinetic parameters. Improvement in bioavailability has been achieved by performing various studies with clinical studies. For future research work, various changes in the therapeutic dose of drugs have been accounted due to increased demand for the pattern of sustained release and clinical improvement. The phyto-phospholipid complexes' stability is a problem that needs more attention and investigation. Such preparation for storage basically comes under high risk of chemical degradation and formation of complexes. Considering the purity of phospholipids, preparation greater than 90% makes the formulation more pleasing to come under oxidative changes and producing a critical factor for maintaining stability. Zeta potential technique plays a vital role in the formulation stability analysis of particle-particle interaction solid dispersion mixtures and the hygroscopicity determination based on temperature. Through the experimental research work, it has been observed that the phyto-phospholipids complexes become more viscous and absorb more moisture when placed in the open air. According to the research data analysis, it has been determined that in the future all these kinds of parameters like stability have to be more focused on overcoming and providing a fruitful formulation for drug delivery systems. There are no such research reports which can give complete confirmation of mechanisms for the absorption of phyto-phospholipids from different parts of the gastrointestinal tract which should be considered a future challenge. These complexes have a unique property of being a target carrier in the system at reticuloendothelial and inflammatory sites. Thus, these kinds of properties can be developed by controlling particle size. Newer techniques such as optimization of pressure or temperature, supercritical fluid systems, and various other techniques can vary in the size of finished products. The size controlling techniques for products that impart high permeability and retention can favour reaching the drug at pathogenic sites such as tumors, cancer, inflammation, and many other target site-based diseases. Phyto-phospholipids can also be an ef-

fective candidate by binding to antigens and ligands on the cellular structures for the target delivery system. These techniques will communicate the scope of utilization of phyto-phospholipid complexes for the treatment of cancer, rheumatism, and osteoarthritis in the future [35].

CONCLUSION

It has been concluded that phyto-phospholipids or phytosomes are essential tools for enhancing the bioavailability of plant or herbal drugs. This study gives a complete description of the phyto-phospholipids and their future prospective. As far as the potential of phytosomes technology is concerned, it has a great future for use in formulation technology and applications of plant compounds. This technique has effectively solved the issue and has offered a preparation of herbal drugs with sufficient lipid penetrability at higher concentrations and sustained therapeutic levels. Hence, the therapeutic action becomes enhanced, and more prolonged, and detectable. These herbaceous extracts can be standardized accordingly and may be formulated as phytosomes for systematic investigation for any improved potential.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

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