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PHYTO-PHOSPHOLIPIDS COMPLEXES AS A POTENTIAL CARRIER FOR BIOACTIVES HAVING HEPATOPROTECTIVE ACTIVITY

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ABSTRACT

Various Phytoconstituents, despite having excellent bioactivity *in-vitro* fail to produce *in-vivo* actions due to their poor lipid solubility or improper molecular size or destruction in gut their by resulting in poor bioavailability. Phytosomes also known as phyto-phospholipid complexes are novel vesicular drug delivery systems used for enhancing the bioavailability of phytoconstituents present in herbal extracts. The phytosomes process produces a little cell due to which the important phytoconstituents of herbal extracts are protected from destruction by the digestive enzymes and bacteria present in gut. They offer better pharmacokinetics and pharmacodynamic properties and result in improved bioavailability than the conventional drug delivery systems. So the present review discusses the various techniques and additives used in the formulation and characterizations of phytosomes, Phytoconstituents have different pharmacological activities such as anti cancer, anti inflammatory, anti his taminic, anti oxidants, wound healing and hepotoprotective activity. With this point of view presented review also focus on various commercial formulations of phytosomes with their applications and their advantages over conventional formulations. Phosphatidyl choline used in the formulation of phytosomes has got additional therapeutic benefit of having hepatoprotective effect. So, when phosphatidylcholine is taken by the patient, it will show the synergistic effect to protect the liver with this aspect we also discuss the role of phytosomes in hepatoprotection.

Key words: Phytosome, Hepatoprotection, Phyto-phospholipid complex, phytoconstituents, herbal extracts.

Introduction

The drug delivery system used for delivering the herbal medicines to the patient is long-established and outdated, resulting in poor efficacy of the drug. If the concept novel drug delivery technology is made functional in herbal medicine, it may help in increasing the efficacy and reducing the side effects of various herbal bioactive and extracts. This is the basic rational of adopting novel method of development for drug delivery in herbal medicines. For a long time herbal medicines were not considered for development as novel formulations owing to lack of scientific justification and lack of processing techniques, such as standardization, extraction and identification of individual drug components in complex poly herbal mixture. However, modern phytopharmaceutical research can challenge these scientific needs such as determination of pharmacokinetics, mechanism of action, site of action, accurate dose required and isolation of specific constituent form complex mixture etc. of herbal medicines required to be successfully incorporated into variety novel drug delivery systems, such as nanoparticles, microemulsions, phytosomes, matrix systems, solid dispersions, liposomes, solid lipid nanoparticles and so on. Phytosomal delivery systemis a patented technology developed by Indena, a leading Pharma manufacturer of drugs and nutraceuticals, to incorporate standardized plant extracts or water soluble or polar constituents to produce lipid compatible molecular complexes and improve their absorption and bioavailability. Phytosomes, complex of natural active ingredients and phospholipids, increase absorption of herbal extracts when applied topically or orally. Phytosomes are cell like structures which result from reacting the phospholipids with the standardized extract or polyphenolic compounds (likeflavonoids, terpenoids, tannins, xanthones) in a non-polar solvent, which are better absorbed, utilized than conventional herbal extracts (Gandhi *et al.,* 2012l Kumar, 2017). Phospholipids are the main building blocks of life and are one of the major components of cellular membranes. In general, they are considered as natural digestive aid and carriers for both polar and non-polar active substances (Tripathy, 2013).

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Most of phospholipids have got additional nutritional benefits, like phos-phatidylserineacts as a brain cell nutrient, useful in liver cell regeneration and itself act as bioactive nutrient showing clinical effectiveness in liver disease including alcoholic hepatic steatotis and drug induced liver damage. In this contextphytosomal technology have been applied to many herbal extractshaving hepatoprotective activity such assilybummarianum Ginkgo biloba, grape seed, olive fruits and leaves, milk thistle, green tea, ginseng, kushenin, marsupsin and curcumin (Lu, 2019). Liver is an important organ involved in the maintenance of hemostatis, production of bile, excretion of bilirubin; cholesterol, hormones and drugs therefore maintenance of healthy liver is the need of every individual. Important functions of liver are summarized in fig. 1.

Hepatotoxicity and Liver Damage

Hepatotoxicity means "damage to the liver caused by any drug or chemical". The liver is prime target of xenobiotics, oxidative stress and toxicity induced by various therapeutic agents, as it plays a vital role in the metabolism and clearance of these chemicals. Such chemicals when taken in a high dose can damage the liver. Free radicals formed in various physicochemical reactions attach the liver cell and results in cell necrosis. Exposure to these metabolic reactions and hazardous chemicals make liver susceptible to different types of diseases, such as acute or chronic inflammation, toxic drug induced hepatitis, cirrhosis and hepatitis due to viral infection (Shakeri, 2016).

Mechanism of liver damage

The various pathophysiological mechanisms of drug induced hepatotoxicity are proposed bo that hepatocellular as well as extracellular level. These include a poptos is of the hepatocytes via extrinsic and intrinsic pathway, disruption of transport proteins associated to bile acid flux, cytolytic t-cell activation, mitochondrial disruption, bile duct injury etc. Most of hepatotoxic compounds disturb the normal functioning of liver cells by causing lipid peroxidation and other oxidative damages. Dose dependent hepatotoxicity is caused due the administration of single toxic dose for a long period of time (Semalty, 2007). The biotransformation of drugs involves the conversion of lipid soluble compounds to more water-soluble compound that can be rapidly washed out of the body. But sometimes this may even lead to the development of rashmetabolites that can interact with nucleic acids, cellular proteins, and lipids, resulting into DNA damage, loss of protein function and lipid per oxidation. Formation of rash metabolite of drugs can also activate the adaptive immune response and produce oxidative stress by damaging the intracellular organelles, additionally excessive intake of alcohol, advanced age, heavy dose of hypolipidemic drugs, drug-drug interactions and previously active any other liver disease are the other contributing factor in hepatotoxicity.

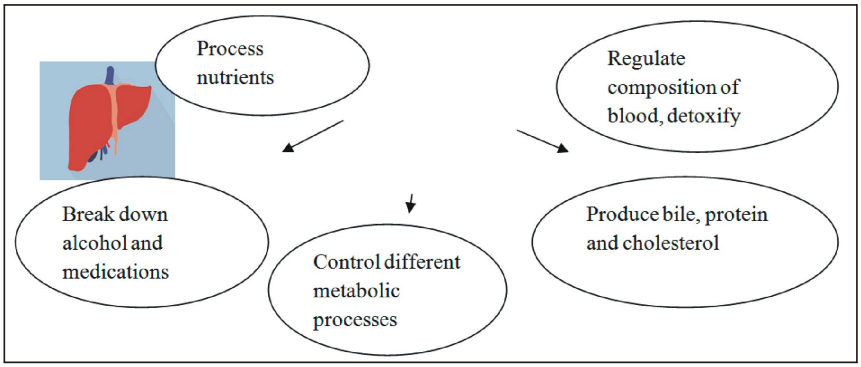

Fig. 1: Summary of Important functions of liver.

Mechanism of Hepatoprotection by herbal therapy

Herbal drugs exert heptoprotection action through multiple effects. Phyto-constituent used in the management of hepatotoxicity regulates and strengthen the functioning of liver, gastro intestinal and boost up our immune system. They protect the liver cells from toxic materials including drugs, lipid per oxidation and injury by free radicals that decrease inflammation and further damage to liver (Chivte, 2017). Improvement in the functioning of gastrointestinal tract may reduce constipation and prevents the absorption of toxic substances which indirectly reduce ascites. They suppress activity of enzyme CYP2E1 which metabolizes most of the drugs into their toxic compounds. They shield normal structure of mitochondrial membrane to augment the activity of enzyme ATPase present in mitochondria. Immune dysfunction is also noticed in liver disease and therefore immune modulatory actionexerted by herbal constituents reduces oxidative stress, inflammation, strengthen and detoxify the liver cells (Jadhav, 2012).

Hepatoprotective Plants

The use of natural remedies have been used for the treatment of liver diseases since ancient times and medicinal plants and principal constituents isolated from them are used globally in one form or another for the samere as on. Liver protective plants contain a variety of bio active molecules like phenols, flavonoids coumarins, monoterpenes, glycosides, alkaloids and xanthenes as given in fig. 2. Some of the plants having hepatoprotective activity with parts used and hepatotoxicity inducing agent used are given in table 1.

Role of Phytosomes in Liver Protection

Most of the bio constituents having hepatoprotective action are flavonoids which are multi ringed compounds and are too bulky to be transported and absorbed by simple diffusion process as a result the ability of this compound to cross lipoid membrane of small intestinal enterocytes is pitiable. Phytosomes are capable of meeting this challenge. Phosphotidylcholine used in the formulation of phytosomes is known to have additional hepatoprotective activity. It has been reported that choline

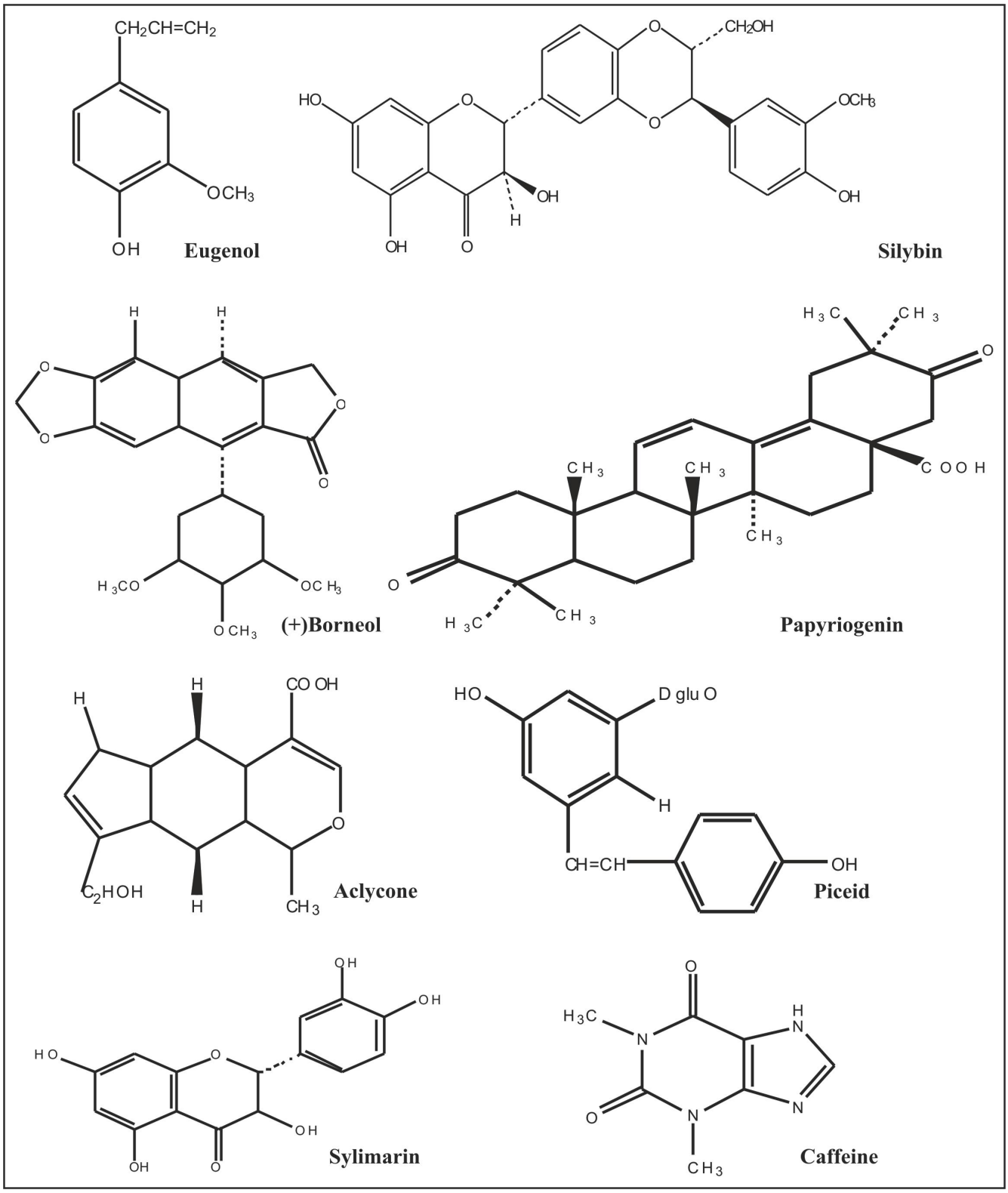

Fig. 2: Phyto-constituents having Hepatoprotective activity.

Table 1: Plants with Hepatoprotective Activity.

Name of the Plant	Part of the Plant used	Extract used	Hepatotoxicity inducing agent	Reference
Phyllanthusmuellarianus	Leaves	Aqueous	Acetaminophene	(Pramyothin, 2007)
PicrorhizaKurroa	Root, Rhizomes	Ethanol	CCl_4	(Shina, 2011)
Bauhinia variegata	Stem bark	Alcohol	CCl_4	(Bodhake, 2007)
Galium aparine	Whole plant	Alcohol	CCl_4	(Bokhari, 2013)
Canna Indica	Aerial parts	Methanol	CCl_4	(KumarT, 2011)
Ficus cordata	Roots	Methanol/ ethyl acetate	CCl_4	(Joshi, 2009)
Curcuma longa	Rhizome	Ethanol	PCM	(Hubert, 2011)
EcliptaProstrata	Fresh leaves	Methanol	CCl_4	(Salama, 2013)
Dodonaeaviscosa	Leaves	Methanol	Alloxan	(Dheeba, 2012)
Cyathea gigantea	Leaves	Methanol	PCM	(Ali, 2013)
Leptadeniapyrotechnica	Whole plant	Methanol, petroleum ether, chloroform, acetone and aqueous	PCM	(Kiran, 2012)
Tylophoraindica	Leaves	Methanol	CCl_4	(Raish,2016)
Opuntia ficus -indica	Leaves	Aqueous	CCl_4	(Mujeeb, 2009)
Vitis vinifera	Leaves	Alcohol	CCl_4	(Zouhir, 2015)
Cinnamomum cassia	Bark	Ethanol	Dimethylnitrosan	(Oman, 2007)
Pistacia lentiscus	Gum	NA	CCl_4	(Eidi, 2012)
Cucurbita maxima	Aerial parts	Methanol	CCl_4	(Sana, 2020)
Calendula officinalis	Whole plant	Methanol	Acetaminophen	(Saha, 2011)
Trigonella foenum-graecum L.	Leaves	Ethanol	CCl_4 Hydrogen peroxide	(Ashwalayan, 2018)
Cassia fistula	Seeds	Methanol	PCM	(Oner, 2008)
Ficus carica	Leaves, fruit and roots	Methanol, petroleum ether, aqueous extract.	Rifampicin	(Bhakta, 1999)
Phyllanthus emblica	Fruit	NA	CCl_4	(Krishna, 2007)
Hibuscusrosasinensis	Flower	Aqueous	Mixture of chloroform and cholic acid with coconut oil	(Srirama, 2012)
Ocimumgratissimum	Fresh leaves	Methanol	CCl_4	(Mishra, 2009)
Mimosa pudica	Leaves	Methanol	CCl_4	(Vilas, 2010)
Saururuschinensis	Whole plant	Ethanol	CCl_4	(Kumaresan, 2015)
Tecomellaundulata	Aerial parts	Aqueous/ ethanol	PCM	(Wang, 2009)
Stachytarphetajamaicensis	Whole plant	Ethanol	CCl_4	(Patel, 2011)
Thymus linearisr	Leaves	Aqueous	CCl_4 and PCM	(Globale, 2011)
Glycyrrhiza glabra	Roots	Aqueous	CCl_4	(Ahmad, 2014)
Convolvulus arvensis	Whole plant	Ethanol	PCM	(Al-Razzuqi, 2012)

is required for the normal functioning of the liver (Qadir, Ali, 2013). Choline is also known to increase the hepatic collagenase enzyme activity and therefore help in preventing fibrosis and cirrhosis. Lecithin has been also reported to have protective effect on non alcoholic fatty liver disease. Thus it has additional protective activity in liver functioning. Some of the commercially available phytosomal formulations indicated for hepatoprotection are listed in table 2. (Saraf, 2013).

Avdantages of Phytosomes as delivery system:

1. Improved therapeutic benefit of complex edphyto-constituents. Various studies indicated that phytosomes increase the absorption of phyto-constituents through oral and topical route of administration and therefore increase bioavailability and reduces the required dose.

2. Improved percutaneous absorption. A Phyto-phospholipid constituent undergoes transition from

Table 2: Commercial Formulations of Phytosomes Available in Market.

Commerical Formulation	Daily Dose	Uses
Grape Seed Phytosomes **(*Thorne Mediclear Plus)***	50 to 100 mg	Beneficial for eyes, lungs, diabetes, varicose veins and
Green Tea Phytosomes ***(Pure medicines)***	50 to 100 mg	Anti-cancer, antioxidant, antimicrobial, cholesterol lowering, blood thinning
Ginkgo biloba Phytosomes ***(Indena)***	120 mg	Improves blood circulation to brain and enhance memory
Siliphos™ ***(Thorne Research)***	120 mg	Beneficial for liver, skin and antioxidant.
Milk Thistle Phytosomes (***Nature's Bounty Milk Thistle***)	150 mg	Maintenance of healthy liver, Antioxidant.

hydrophilic background to lipophilic conditions of lipoidal membrane to enter the cells and improve percutaneous absorption of active constituent. Due to this characteristic they find application in transdermal drug delivery systems.

3. Provide additional hepatoprotective effect. Phosphotidylcholine used in the formulation of phytosomes act as hepatoprotective and provide synergistic action in liver protection because cholin is required for the normal functioning of liver.

4. Improvement in the stability of complexed constituents because of formation of chemical bond between phyto-constituent and phospholipid.

5. Improved liver targeting by increasing the solubility of active constituent in bile.

6. Imparts sustained and prolonged effect of enclosed compound therefore suitable for drugs having short half life for example Naringenin.

7. Improved patient compliance by reducing the dose frequency.

Properties of Phytosomes

• Chemical Properties:

Phytosome are the complex between phospholipids and phytoconstituents. These complex are formed as result of formation of hydrogen bond between the polar head of phospholipids and polar group present on the phytoconstituent. In the presence of hydrophilic environment they form mecillies like structure very similar to the liposomes but unlike liposomes in case of phytosomes the phyto-constituent get entrapped within the polar head of the phospholipid and became integral part of the membrane (Mei *et al.*, 2019).

• Biological Properties:

Phytosomes are the novel drug delivery systems used as an carriers for active herbal constituents. Enhanced bioavailability of phyto-phospholipid complexes over the conventional formulation is demonstrated due to improved pharmacokinetic and pharmacodynamic properties of the phyto-phospholipid complexes (Patel, 2009).

• Formulation technique for Phytosomes:

Phytosomes are prepared by reacting two or three moles of phospholipids of natural or synthetic origin with one mole of bioactive molecule taken in organic solvent. This resulting solution was dried by evaporating the solvent and thin film so formed was hydrated in the presence of water or buffer. The suspension formed is recovered as phytosomal suspension this technique is known as solvent evaporation technique. Steps involved in the solvent evaporation method are demonstrated in the fig. 3. Other methods used include anti solvent precipitation and lyophilization technique. (Kumari, 2011).

Characterization of Phytosomes

• *Yield of thephyto- phospholipids complex:*

Percentage yield of the phyto-phospholipids complex produced can be analysed by calculating the difference in the weight of initial phyto-constituent and free Phyto-constituent after the formation of complex. This will give the amount of the phyto-constituent involved in the complex formation.

$$\% \text{ Yield} = \frac{\text{Initial}_{wt} - \text{Free}_{wt}}{\text{Initial}_{wt}} \times 100$$

The % age yield of complex formed depends on numbers of factors such as solvent used, molar ratio of phyto-constituent and phospholipid taken, duration of hydration and temperature used. Analytical techniques such as high performance liquid chromatography, ultraviolet spectrophotometry can be used to estimate the amount of phyto-constitutent involved in complex formulation. (Saraf, 2010).

• *Partition coefficient and solubility analysis:*

The lipophilicity and hydrophilicity of phtyo-constituent and phyto- phospholipid complex formed can be estimated by solubility analysis in water and organic solvent and partition coefficient in N-octanol/ Water. Since phytosomes improves solubility therefore Phyto-phospholipid complex formed should give greater and improved lipophilicity and hydrophilicity than phytoconstituent alone. (Marena, 1991).

• *Particle Size determination:*

Particle size and size distribution are need to assessed as they are significant from view point the stability of the complex formed. The average particle size of the phytosomes lies in the range of 50nm to 100µm. Particle size and size distribution can be assessed by zeta potential value measured using Malvern particle size analyzer. (Amin, 2012)

• *Surface Morphology of the complex:*

Solid state properties and surface morphology of the complex formed can be studied using scanning electron microscopy (SEM). (Rathore, 2015) Vesicular structure of phyto-phospholipid complex can be interpreted through transmission electron microscopy (TEM).

• *Spectroscopic Analysis:*

Samples that illustrate different absorption in the UV wavelength range can be used to differentiate structural properties of a compound. Any differences in the UV absorption characteristics of phyto-constituent before and after complex formation can be recognized using UV spectra. In general chromophores of compounds are not affected on complex formation with phospholipids. (Singh, 2014)

• *Differential scanning calorimetry (DSC):*

Any kind of incompatibility between phyto constituent and phospholipid can be pointed out in terms of appearance of new peaks and disappearance of original peaks, change in melting point and relative peaks area in differential scanning calorimetry (DSC) curve. Phyto-phospholipid complexes typically present sharp characteristic peaks compared to those of a simple physical mixture. (Kulkarni, 2011)

• *Fourier transform infrared spectroscopy (FTIR):*

FTIR analysis is another analytical technique used to study phyto constituent and phospholipid interaction, different functional groups elicit distinctive characteristics peak at wave number, position, shape, and intensity. The formation of phyto-phospholipid complexes can be demonstrated by comparing the FTIR spectra of phospholipid, phytoconstiuent alone and physical mixtures to that of complex formed. (Kidd, 2009)

• *X-ray diffraction*:

X-ray diffraction is an valuable technique used to carry out structural interpretation of both crystalline and some amorphous materials. This analytical tool is generally performed on either phyto-constituents or phyto-phospholipid complexes and their physical mixtures. X-ray diffraction of an phyto- constituent and physical mixture shows strong crystalline peaks that indicate a highly crystalline form,. on the other hand, phyto-phospholipid complexes do not exhibit crystalline peak,

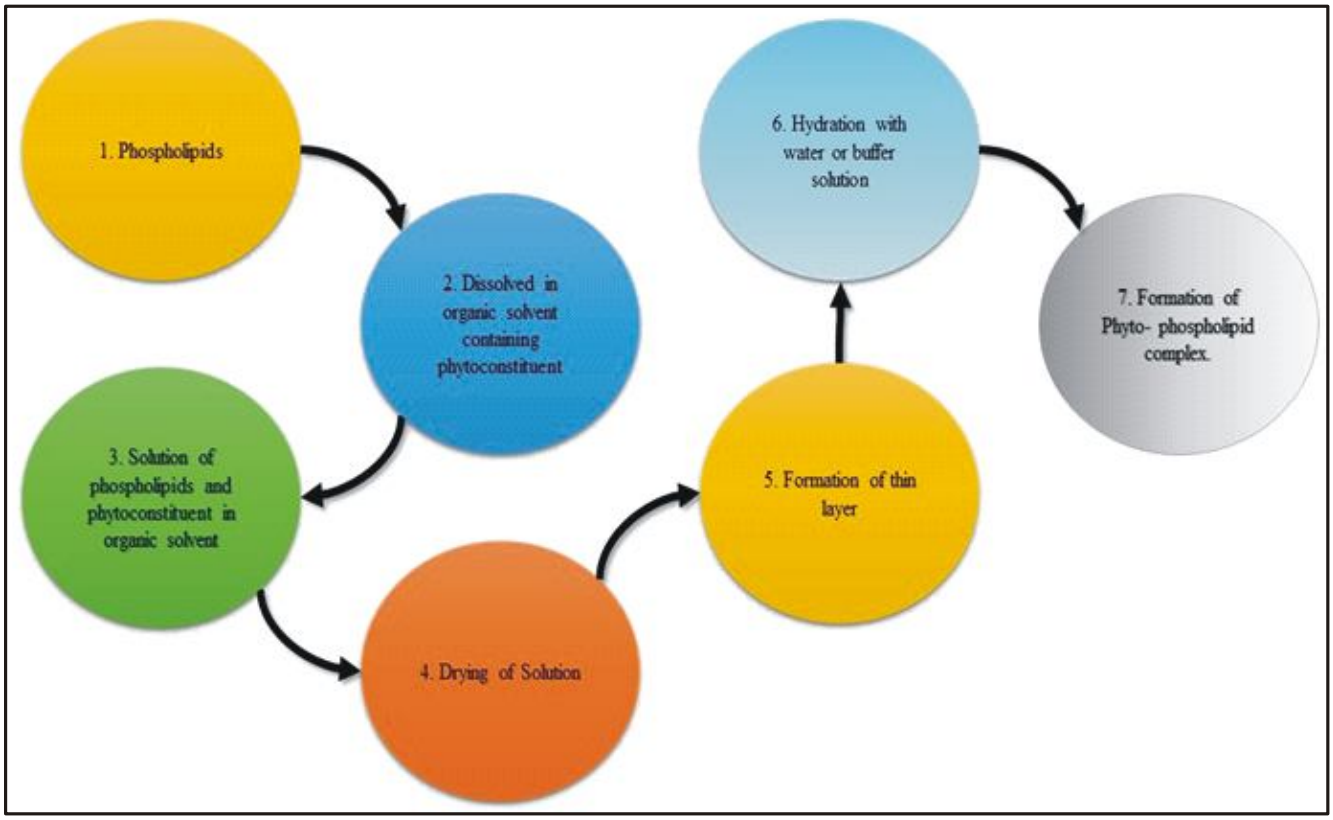

Fig. 3: Steps involved in the preparation Phyto- Phospholipid complex (Phytosomes).

which suggests that the phyto-constituents in complexation with phospholipids exhibit a molecular or amorphous form because of this reason the phyto-phospholipid complexes show better lipophilicity and hydrophilicity than phyto-constituents alone. (Das, 2020).

• *Nuclear magnetic resonance spectra:*

Nuclear magnetic resonance spectroscopy (NMR) is an important analytical technique used to interpret the structures of the complexes. The interactions between polyphenols and phospholipids are created by hydrogen bonds rather than chemical bonds. From NMR spectra one can study that the fatty acid chain in case free phospholipid and complexed from give unchanged signals. (Singh *et al.*, 2011) The spectral analysis of phyto-phospholipid complexes suggests that the aliphatic side chains get wrapped around the central choline-bioactive parts of complexes, therefore imparting lipophilic character. (Sharma, 2016).

In Vitro and *In Vivo* Characterization

In vitro and *In vivo* evaluation of phytosomes can be done using different models selected on the basis of therapeutic and biological activity of the phyto-constituent. For the determination of *in vitro* hepatoprotective effect antioxidant and free radical scavenging activity of phytosomes is assessed and *in vivo* hepatoprotective the effect of prepared phytosomal complex can be evaluated on animals against thioacetamide, paracetamol or alcohol induced hepatotoxicity. (Tung, 2017) *In vitro in vivo* assay of hepotoprotective assay of using phytosomes is shown in fig. 4.

Recent work done on Phytosomes with Hepatoprotective Phytoconstituents

Sonam Sharma *et al.,* worked on formulation and characterization of phytosomes containing ethanolic extract of *Abutilon indicum* and *Piper longum* to in order to have better effectiveness and safety. Results of study indicated that combined extract has shown

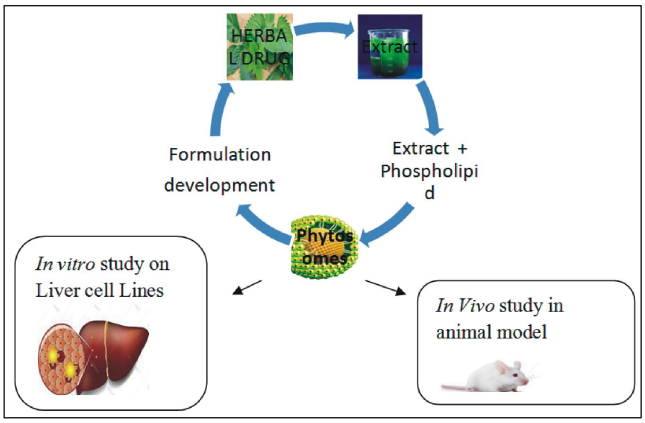

Fig. 4: *In vitro-in vivo* assay of hepatoprotective activity.

hepatoprotective activity but phytosomal formulation has more effective hepatoprotective action on CCl_4 induced liver toxicity at very low dose comparative to a higher dose of combined extract. (Gahandule, 2016).

Bui Thanh Tung developed a phytosomal curcumin complex and evaluated the hepatoprotective effect of phytosome curcumin complex on paracetamol induced liver toxocity in mice. Results showed that phytosome has stronger hepatoprotective effect compared to plain curcumin extract. The study suggested that phytosome curcumin complex has strong antioxidant activity and hepatoprotective effects. (Naveen, 2019).

Gahandule, M.B. carried out formulation and development of hepato-protective butea monospermaphytosome. Phytosomes were successfully prepared and complexed. It showed extended release drug release property with enhanced free radical scavenging activity. (Kuntal, 2005)

Mascarella, evaluated the protective effect of ethanolic and aqueous extract of *Turneraaphrodisiaca* leaves against carbon tetrachloride (CCl_4)-induced liver damage in male wistar rats. The results suggested that ethanol and aqueous extract of *Turneraaphrodisiaca* leaves acts as a strong hepatoprotective agent against CCl_4 induced hepatotoxicity in rats. (Mascarella, 1993).

Suresh *et al.*, formulated the Quercetin-phospholipid complex by a simple and reproducible method and also showed that the complex formed produce better hepatoprotective effect than the alone Quercetin in rat liver injury induced by carbon tetrachloride. (Suresh *et al.,* 2008).

Moscarella *et al.,* conducted study onchronic hepatitis patients (viral, alcohol or drug induced) treated with silybinphytosome complex at a dose of 120 mg either twice daily or thrice daily for upto 4 months, liver functioning get normalized in patients treated with silybin phytosome compared to untreated patients (Mascarella, 1993).

Suresh, R.N. *et al.*, studied protective effect of *Ginkgoselect* phytosomes in rifampicin induced hepatotoxicity. The mechanism involved in the induction of protective effect was studied in rats. The results of investigations suggested that the hepatoprotective effect of *Ginkgoselect* phytosomes may be due to its antioxidant and free radical scavenging activity (Suresh *et al.,* 2008).

Conclusion

Thorough the study of literature it has been found that active constituents present in plants have significant therapeutic potential to treat liver disease andphyto-

phospholipid complexes formed out of these have ability to promote their therapeutic properties when compared with the conventional plant extracts. Phytosomes can be developed for different therapeutic purposes like hepatoprotective, cardiovascular, liver diseases, anti inflammatory, immunomodulator, anticancer, anti-diabetic etc or for prophylactic and health purposes as nutraceuticals, in due course.

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