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Phytophospholipid Complexes: A Potential Novel Carrier System for Hepatoprotective Drug Delivery System

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ABSTRACT

A variety of huge number of phytoconstituents isolated from the parts of plant or whole plants having the wide spectrum of pharmacological activity. But these phytoconstituents, despite having excellent in vitro bioactivity, but fails to show no in vivo activity actions, due to their limited lipid or aqueous solubility, Improper molecular size, improper permeation through biological mucosa or destruction in gastric or gut environment. So that the potential use of these herbal based drugs are limited due to their poor absorption and poor bioavailability after topical or oral administration. Over the past century, the great advancement has been made for development of novel drug delivery systems (NDDS) of phytoconstituents and herbal extracts such as Nanotechnology based formulation, liposomes, niosomes, transferosomes, ethosomes Phytophospholipid complex (phytosomes) and microparticle, etc has been developed. Novel potential phytophospholipid complexation methods have been developed by the formulation researcher to enhance the therapeutic activity of plant based drugs. In this method complexation of phytoconstituents with phospholipids in different molar ratio results into the development of novel herbal drug delivery system "phytophospholipid complex". From the earlier research the formulation scientists have been proved that phytophospholipid complex show better pharmacokinetic and pharmacological profile than conventional herbal extracts. This review article highlights about the phospholipd as a carrier, current and future scenario of phytophospholipid complex and its potential application in hepatoprotection.

Keywords: Herbal Drug Delivery, Phospholipis, Phospholipid Complex, Hepatotoxicity, Hepatoprotection

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INTRODUCTION

Naturally occurring herbal drugs or Plants based derived drugs gained advantages and popularize in the global markets as a safer and effective substitutes of synthetic drugs which are considered to be full of adverse and toxic interactions. Currently, one-third to approximately one-half of presently available drugs are generally derived from plants or other natural sources [1, 2].

However, huge number plant active molecules isolated from plants are poorly absorbed by oral route, which limits their widespread application[3, 4]. The poor absorption of these phytocompounds results is mainly due to two inherent properties. First, the multi-ring structures of natural compounds are too large that limits the absorption of drug by passive diffusion or non-active absorption. Second, the poor aqueous or lipid solubility of these phyto compounds prevents the permeation of drug through the outer membrane of gastrointestinal cells [5, 6]. Active phytoconstituents isolated from natural sources have been shown excellent in *vitro* pharmacological activity, but poor *in vivo* performance. So the past few decades, a great advancement and attention has been focused on the development of herbal novel drug delivery system (HNDDS).

However, the poor oral bioavailability of naturally occurring or plant active principles has become the challenging task for formulation researchers. further It has been observed from the past research that poor bioavailability of these compounds are mainly due to the low water or lipid solubility, high molecular weight/size and poor plasma membrane permeability [3,7,8]. Moreover the standardized extracts when given by oral route, lose some of their constituents in the presence of gastric fluids [5].

In herbal drug formulation research, several novel delivery systems have been developed such as nanotechnology based delivery like nanoparticle, lipid based system like liposomes, niosomes, transferosomes, ethosomes, phytophospholipid

complexes etc. These novel carrier systems have a number of advantages for naturally occurring active principles like solubility enhancement and improvement of bioavailability, protection of drug from toxicity, enhancement of therapeutic activity, stability improvement of formulation, improving tissue macrophages distribution, sustained drug delivery, protection of drug from degradation through physical and chemical environment etc. [9]

So the novel technique has been developed by complexing plant actives with phospholipids, this is one of the most successful methods for improving bioavailability and therapeutic potential of a number of poorly absorbed naturally occurring phytoconstituents and their derivatives . The phytophospholipid complexation method was first developed in the year 1989 in Italy by chemically interaction of phytoconstotuents especially polyphenolic extracts with phospholipids containing phosphatidyl choline. The formed complex markedly improves the bioavailability of the polyphenolics when it compared with the bioavailability of pure drug/ extract [10].

This technique employed by utilizing the phospholipid molecules specially, containing phosphotidylcholine to form complexes with phyto constituents which results in improvement of the membrane permeability, water–oil partition coefficient and hence the bioavailability of these drugs [11, 12]. The incorporation of water soluble drugs into their phospholipid complexation, enhanced their bioavailability by increasing permeation through the lipoidal biological membrane while the phospholipid complexation of poorly water soluble drugs improved their bioavailability by increasing their solubility in gastric fluids [13, 14].

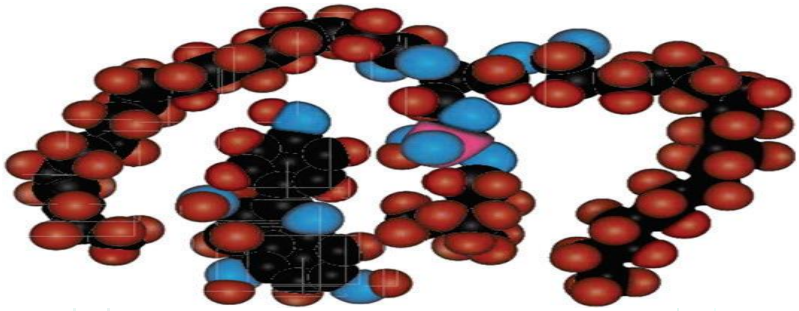

Figure-1 Structure of phytophospholipid molecule[15]

ADVANTAGES OF PHYTOPHOSPHOLIPID COMPLEX

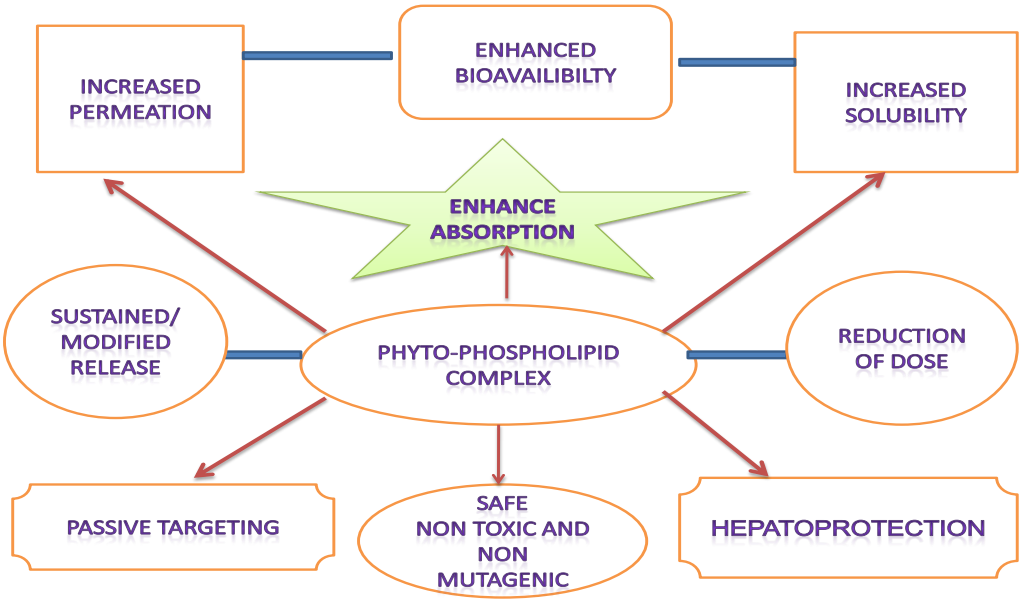

Figure -2 Benefits of phytophospholipd complex

PHYTOPHOSHOLIPID –

there are many so straiges have been developed to improve the bioavailability and therapeutic efficacy of herbal drugs, but one of the novel method that is employed by the complexation of herbal compounds with naturally occurring phospholipid molecules has arisen as a potential novel carrier system for improving the bio-absorption of poorly absorbed phytoconstituents. The phospholipid molecules have unique structural components which are similar to the lipid content of the mammalian cell membrane so that it becomes the highly compatible with the human physiological system [16].

Phospholipids are lipids that contain phosphorus, a polar head potion and non-polar tail potion in their structural back bone.10 Phospholipids are amphiphillic in nature and have the characteristics of excellent biocompatibility because of the similar lipoid structure present in mammalian cell membrane. These unique properties of phospholipids make it more appropriate to be employed as

important pharmaceutical excipients and have versatile applications in development of novel carrier systems.

The mammalian biological membrane constitutes by different classes of phospholipids, like phosphatidyl ethanolamine (PE), phosphatidylinositol (PI), phosphatidylcholine (PC), phosphatidic acid (PA), and phosphatidylserine (PS).[17]

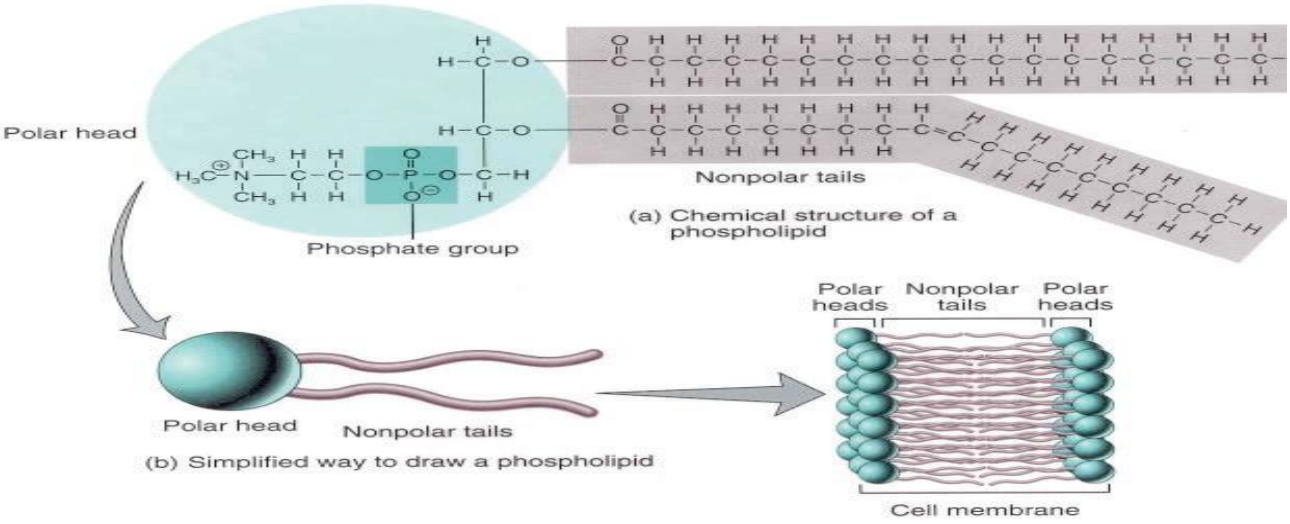

Figure 3- Structure of phospholipid [18]

phosphatidylcholine (PC) contains two neutral tail groups and a positive head group which contains an oxygen atom in the phosphate group that has a strong tendency to gain electrons, while nitrogen is to lose electrons. So this type molecular arrangement, makes PC miscible in both water and lipid environments.[19]

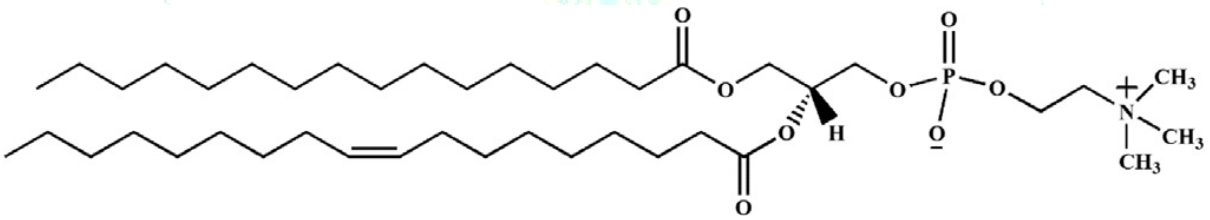

Figure-4 Structure of phosphotidylcholine [20]

THE MAIN SOURCES OF PHOSPHOLIPIDS-

According to the source phospholipids can be classified as natural phospholipids and synthetic phospholipids.

Natural phospholipids

In 1793, a complex aliphatic compounds was identified by Fourcroy. In 1812, Uauquelin first discovered phospholipids in human brain. In 1846, firstly Gobley phospholipids from egg yolk. The term "lecithin" which is derived from the Greek lekithos was first used to describe a sticky orange material that is isolated from egg yolk. After 20 years, choline component in lecithin was determined [21]. Phospholipids are widely distributed in animals and plants,and the main sources are vegetable oils (e.g. soybean, cotton seed, corn oil, sunflower and rapeseed) and animal tissues (e.g. egg yolk and bovine brain). In terms of production, egg yolk and soybean are the most important sources for phospholipids [22].

However, soybean and egg yolk phospholipids are differ in their contents and species of phospholipids, mainly including:

1) Egg yolk lecithin contains a higher amount of PC.
2) Phospholipids present in egg yolk contains long chain polyunsaturated fatty acids of N-6 and N-3 series, primarily arachidonic acid (AA) and docosahexaenoic acid (DHA), which are absent in soybean lecithins;
3) Animal lecithins have characteristic of the presence of sphignomylins SM [23].
4) The saturation level of egg yolk lecithins is higher than that of soybean lecithins [24], so their oxidative stability is better than that of soybean lecithins.
5) In the egg yolk phospholipids, saturated fatty acid is usually at sn-1 position, and unsaturated fatty acid is at sn-2 position [25], while for soybean lecithin, SN-1 and SN-2 position can be both unsaturated fatty acids. For example, dilinoleoylphosphatidylcholine (DLPC) is the main component of soybean phosphatidylcholine (SPC) [26].

Synthetic phospholipids- Scientists and researcher mainly focus on chemical synthesis to obtain single component with defined structure and configuration [27]. The synthesis of phospholipids can be divided into semi synthesis and total synthesis. Semi-synthesis method of glycerol-phospholipids is obtained by changing the head or tail groups or both on

the basis of natural phospholipids and it takes less reaction steps as compared to total synthesis.

The semi-synthetic methods for glycerophospholipids mainly include:

1) Hydrogenation of double bond of natural phospholipid to obtain the saturated phospholipids that have a high melting point and oxidation stability;
2) Acylation of SN-glycero-3- phosphocholine (GPC) obtained by deacylation of natural PC with activated acyl derivative can get the desired PC;
3) Phospholipase D catalyzes glycerophospholipids to generate the phosphatidic acid (PA), and the hydroxy-containing acceptors such as glycerol and serine can attach to PA, which can converse the choline head group into various phosphorylated alcohol head groups.

The total synthesis of glycerophospholipids involves the formation of ester or ether bonds linking apolar moieties to glycerol backbone, and the attachment of polar head group. The synthetic glycerophospholipids have the advantages of single component and stable property.[25].

The procedure for semi-synthesis of sphignomylin SM involves the deacylation of the natural SM extracts (obtained primarily from bovine brains) results in the formation of sphingosylphospocholine further acylated to SM by using the fatty acid of choice. It has been found that during the reaction step of deacylation-reacylation, a significant amount of the L-threo stereoisomer is formed. So that the final product contains the mixture of D-erythro and L-threo stereoiomers [28].

The total synthesis of SM is considerably more complex than that of the glycerophospholipids. So that there are only few studies on the fully synthetic and stereochemically pure SM [28]. The complete or total synthesis of SM includes the following steps: 1) the synthesis of sphingosine, 2) the synthesis of ceramide (N-acylsphingosine), 3) the synthesis of SM [29].

HEPATOTOXICITY AND HEPATIC DAMAGE-

The liver is a vital, largest visceral organ for metabolism and elimination of drugs. Its strategic location and multidimensional functions support almost every other organ in the body. [30, 31]

It also regulates various functions in the body, like metabolism, secretion, storage and detoxification. Hepatic diseases are now a day's very common in developed and developing country. Liver damage is usually associated with the distortion of some of above mentioned functions. After intestinal absorption of drug, the portal vein supplies blood to the liver. So liver is directly exposed to elevated amount of toxic agents [32,33]

Some drugs, when taken in overdoses may cause liver injury for example acetaminophen. Chemicals, drugs or their metabolite that cause liver injury are called hepatotoxins [34]. As per the literature search about 50% of all acute liver failure cases represents a serious clinical problem, are due to drug-induced hepatotoxicity make it.Although the majority of cases of acute liver failure are due to intentional or unintentional misuse, 16% are idiosyncratic [35]. Some examples of inorganic compounds may cause hepatotoxicity are arsenic, phosphorus, copper and iron. Certain naturally occurring plant toxins such as pyrrolizidine alkaloids, fungal toxins and bacterial toxins cause liver damage. [36].

Liver damage can also be caused by certain drugs, especially anti-tubercular drugs, general anesthetics, paracetamol and some anti-cancer drugs.

Toxic hepatitis a serious liver disease caused by severe adverse reaction to antituberculosis drugs, it usually initiates in the first few weeks of treatment along with liver necrosis, further results to encephalopathy and death.

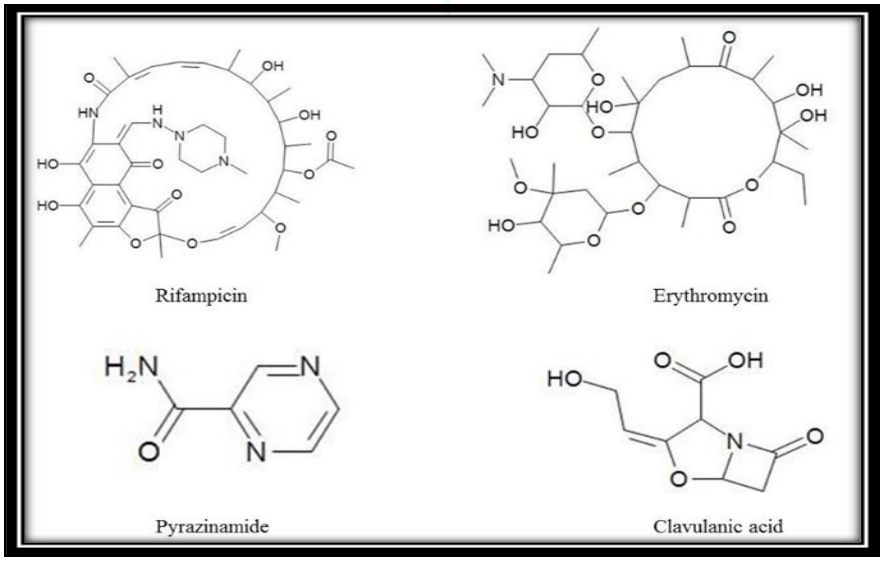

Figure-5 .Structure of some hepatotoxic agent[37]

Cirrhosis (formation of fibrous tissue in liver) caused by excessive consumption of alcohol,is a common occurrence in modern life style. Sometimes Liver can also be damaged by some chemicals such as galactosamine and chloroform [38].

It is not necessary that liver toxicity occurs from direct toxicity of the primary compound but also from reactive metabolite or immunologically-mediated response. This can affect hepatocytes, biliary epithelial cells and liver vasculature [39, 40].

Hepatotoxic response produced by chemicals or drugs or metabolite and toxins mainly depends upon the nature of toxicant, concentration gradient of the toxicant and liver enzymes level in blood .[41]

MECHANISM OF HEPATOTOXICITY

Liver is the main vital organ for metabolism and elimination of drugs.

Most of the drugs (oral) and xenobiotics are lipophilic which enables their easy absorption across intestinal membranes. They are rendered hydrophilic *via* hepatic metabolism and are easily excreted. Exogenous products are metabolized in the liver mainly through phase I and II reactions [42]. The hepatic metabolism involves Phase I and Phase II reactions. Phase I involves oxidative, reductive, hydroxylation and de-methylation pathways, primarily by way of the cytochrome P-450, the most important family of metabolizing enzymes system which is located in the endoplasmic reticulum in the liver. Phase I reactions mostly produce toxic intermediates which are transformed to non-toxic compounds by phase II reactions, usually considered as detoxification pathways. Phase II reactions involve the conjugation of chemicals with hydrophilic moieties such as glucuronide, sulfate or amino acids and lead to the formation of more water-soluble metabolite which can be excreted easily [43]. Further Phase II reaction implicates glutathione which can covalently bind to toxic intermediates by glutathione-S-transferase. However, this phase can also lead to the formation of unstable precursors of reactive species that can cause hepatotoxicity [44, 45, 46].

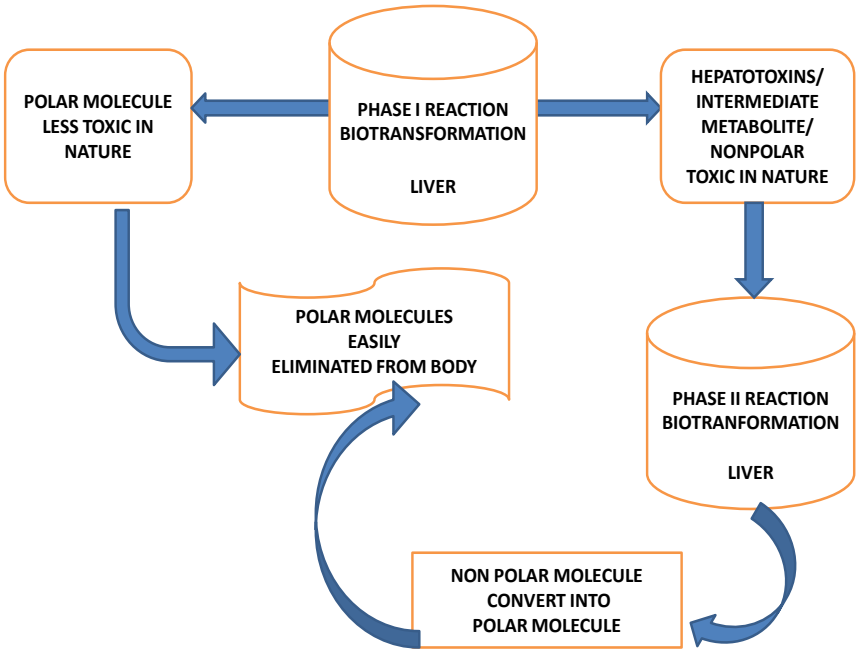

Figure -6 Metabolisms of hepatotoxins /xenobiotics in liver.

TARGETING OF PHYTOLIPID BASED SYSTEM

Phospholipids are the main source of phosphatidylcholine and choline, both the molecules of phospholipids liquefy the fat dumped inside the liver in the case of hepatic steatosis or fatty liver and also show some other hepatoprotective effects[47]. From the literature survey it was found that soya phospholipids are hepatoprotective in nature and prevent liver damage by alcohol, drugs abuse or drug induced and other toxins [48]. They have also been reported to aid in clearance of serum cholesterol and increase circulating HDL levels in plasma [49].

Targeting of phyto molecules at a particular site or specific organ is a very challenging task for the researchers that for therapeutic response it is necessary that specified amount of drug should reach to the target site to and retain for the desired duration. However, Phyto-lipid based vesicle system facilitates the liver targeting (Figure 1) by increasing the solubility in the bile salts. The targeting can also be achieved by attaching ligand in the site with right orientation for binding to the target receptors e.g. Monoclonal antibodies must bind to the drug carrier system with their Fc part, so that their antigen binding site (Fab) is free to interact with the antigenic [50,51,52]

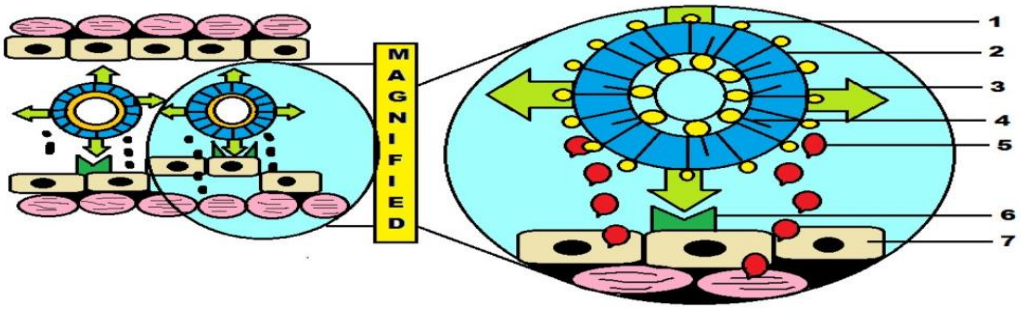

Figure-7- Targeting of drug to parenchymal cells (hepatocytes) of liver using ligand - 1 PC head - 2-Phyto-vesicles 3- Ligand molecule, 4- PC tail [53]

HEPATOPROTECTIVE POTENTIAL OF PHYTOPHOSPHOLIPID COMPLEX

Pifferi (1991) concluded that silybin phospholipd complex given orally shows higher pharmacological activity in animal models of hepatic injury. Further result obtained that oral bioavailability and specific organ targeting nature of silybin phospholipd was found to be much greater than that of silybin administered as a component of silymarin[54].

Bombardelli et al. (1991) investigated that Silymarin, standardized mixture of flavanolignans isolated from the fruits of S. marianum was complexed with phospholipids. The complex showed much higher specific activity and a long lasting action than the components, with respect to per cent reduction of odema, inhibition of myeloperoxidase activity, antioxidant and free radical scavenging properties[55].

Conti et al. (1992) tested IdB1016 (silybin-phosphatidylcholine) in rodents in different models of liver damage. After oral administration, silipide exhibited a significant and dose related protective effect against the hepatotoxicity induced by CCl4, praseodymium, ethanol and galactosamine. Unlike the silybin and Phosphatidylcholine, in the same dose the complex IdB1016 showed protective activity against paracetamol induced hepatotoxicity [56].

Buzzelli et al. (1993) a pilot study was carried out for liver protective effect of silybin-phosphatidylcholine complex (IdB 1016) in chronic active hepatitis (CAH), and it was found that IdB1016 that complex formulation improve liver function test related to hepatocellular necrosis and/or increased membrane permeability in patients offered by CAH [57].

Carini et al. (1992) corelated that the addition of increasing concentrations of IdB 1016 to isolated rat hepatocytes caused a dose-dependent inhibition of lipid peroxidation induced by cumene hydroperoxidase. Further it was concluded that IdB 1016 acted as potentially useful protective agent against free radical mediated toxic liver injury [58].

Vailati et al. (1993) performed a phase-II randomized open trial to clinically evaluate the dose response relationship of IdB 1016 in patients with viral or alcoholic hepatitis. It was found that treatment with IdB 1016 showed improvement in dose dependent manner[59].

Busby et al. (2002) concluded from the study that silymarin phytosome showed a better hetoprotectant activity from ethanol-induced behavioral deficits than pure silymarin [60].

Tedesco et al (2004) investigated silymarin loaded phytosome exert better antihepatotoxic activity than silymarin alone and it can also provide protection against the toxic effects of aflatoxin B1 on performance of broiler chicks [61].

Maiti et al.,(2005) developed the quercetin–phospholipid complex by a simple and reproducible method and also showed that the formulation exerted better therapeutic efficacy than the molecule in rat liver injury induced by carbon tetrachloride[62].

Yanyu et al (2006) developed the silymarin loaded phytosome and studied pharmacokinetic parameters in rats.from the study it was found that the bioavailability of silybin-phospholipid complex was increased remarkably after oral administration than the silybin alone in rats .this is due to increase lipophilic property of silybin-phospholipid complex and further improvement of the biological effect of silybin [63].

CONCLUSION

The challenges regarding phytopharmaceuticals in the area of liver related problems is very much in demand to generate new therapeutic entity or dosages form development. A lot of phytocomponds have been isolated and some are in pipeline but all these having excellent in vitro action but fails to produce in vivo because of their physicochemical inherent property which limits the opportunity to generate carrier system containing plan components. So phyto-phospholipid complexation approache has offered a preparation of herbal drugs that have sufficient lipid penetrability, higher concentration at the site of absorption and sustained therapeutic levels in plasma with a slower rate of elimination.

Apart from this, the unique carrier system utilized that is Phospholipids, as one of the most promising novel material, which can be exploited intelligently and effectively to target liver related disorders and diseases as well as its protection. The prepared complex increases the solubility of phytocompound in water or lipids make them excellent carrier system for improving the bioavailability of herbal drugs.

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