Pharmacognosy Reviews
Vol 1, Issue 2, Jul-Dec, 2007

PHCOG REV.
An official Publication of Phcog.Net

Phcog Rev.: Short Review
The Phyto-phospholipid Complexes- Phytosomes: A Potential Therapeutic Approach for Herbal Hepatoprotective Drug Delivery

Ajay Semalty[*1], Mona Semalty[2] and M.S.M. Rawat[3].

[1]*Department of Pharmaceutical Sciences, H.N.B. Garhwal University Srinagar (Garhwal)-246174 (India);*
[2]*Department of Chemistry, H.N.B. Garhwal University Srinagar (Garhwal)-246174 (India);*
Author for correspondence: semaltyajay@gmail.com*

ABSTRACT

A large number of herbal drugs possess the wide spectrum of therapeutic activity. But the potential use of these herbal drugs is limited due to their poor absorption and poor bioavailability after oral administration. The bioavailability can be improved by the use of delivery systems, which can enhance the rate and the extent of drug solubilizing into aqueous intestinal fluids as well as the capacity to cross the lipid rich biomembranes. Phospholipid based drug delivery systems have been found promising for the effective and efficacious herbal drug delivery. Complexing the polyphenolic phytoconstituents in molar ratio with phosphatidylcholine results into a new herbal drug delivery system- "Phytosome". Phytosomes show better pharmacokinetic and therapeutic profile than conventional herbal extracts. This article reviews the current status of phytosomal research and its potential application in hepatoprotective and antihepatotoxic activity.

KEYWORDS: Phytosome, phospholipid complex, herbal drug delivery, phosphatidylcholine.

INTRODUCTION

Most of the bioactive constituents of herbal drugs are water soluble molecules However, water soluble phytoconstituents like many flavonoids are poorly absorbed(1) either due to their multiple-ring large size molecules which can not be absorbed by simple diffusion, or due to their poor miscibility with oils and other lipids, severely limiting their ability to pass across the lipid-rich outer membranes of the enterocytes of the small intestine.

Water-soluble phytoconstituent molecules (mainly polyphenoles) can be converted into lipid-compatible molecular complexes, which are called phytosomes. Phytosomes are more bioavailable as compared to simple herbal extracts owing to their enhanced capacity to cross the lipid rich biomembranes and finally reaching the blood(2). The lipid-phase substances employed to make phytoconstituents, lipid-compatible are phospholipids from soy, mainly phosphatidylcholine (PC). PC, the principal molecular building block of cell membranes, is miscible both in water and in oil/ lipid environments, and is well absorbed orally. Phospholipids are small lipid molecules in which the glycerol is bonded only to two fatty acids, instead of three as in triglycerides, with the remaining site occupied by a phosphate group(3).

The term "*phyto*" means plant while "*some*" means cell-like. What the Phytosomes process produces is a little cell, whereby the valuable component of the herbal extract is protected from destruction by digestive secretions and gut bacteria(4).

The phytosome process has been applied to many popular herbal extract including *Ginkgo biloba*, grape seed, hawthorn, milk thistle (*Silybum marianum*), green tea (*Thea sinensis*) and ginseng (*Panax ginseng*). The flavonoid and terpenoid components of these herbal extracts lend themselves quite well for the direct binding to phosphatidylcholine. The present article reviews the various aspects and the latest trends of phytosomal research on a variety of plant materials for potential therapeutic uses.

Properties of phytosomes

Phytosomes results from the reaction of a stoichiometric amount of the phospholipid with the selected polyphenol (like simple flavonoids) in a nonpolar solvent(2). They are lipophillic substances with a definite melting point, freely soluble in nonpolar solvents (in which the hydrophilic moiety was not), and moderately soluble in fats. When treated with water, they assume a micellar shape, forming structures which resemble liposomes, but which exhibit fundamental differences. In liposomes, the active principle is dissolved in the medium of the cavity or in the layers of the membrane, whereas in the phospholipid-flavonoid compounds it is an integral part of the membrane (Fig. 1). Molecules are anchored through chemical bonds to the polar head of the phospholipids, as can be demonstrated by specific spectroscopic techniques(5,6).

Unlike phytosomes, a liposome is formed by mixing a water-soluble substance with Phosphatidylcholine. No chemical bond is formed; the Phosphatidylcholine molecules surround the water soluble substance. There may be hundreds or even thousands of Phosphatidylcholine molecules surrounding the water-soluble compound. In contrast, with the phytosomes process the Phosphatidylcholine and the individual plant components actually form a 1:1 or a 2:1 complex depending on the substance. This difference results in Phytosome being much better absorbed than liposomes.

Methods of preparation

Phytosomes are prepared by complexing polyphenolic phytoconstituents in 1:2 or 1:1 ratio with phosphatidylcholine. Mareno and Lampertico (1991), Jiang *et al.* (2001), Maiti et al (2006) and Maiti et al (2006) reported the methods of Phytosome prepration(7-10).

Yanyu *et al* (2006) prepared silybin-phospholipid complex using ethanol as a reaction medium. Silybin and phospholipids were resolved into the medium, after the organic solvent was removed under vacuum condition, silybin-phospholipid complex was formed(11).

Figure 2 shows the formation of Silymarin Phytosome from the three main constituents of Silymarin (milk thistle) extract. Silybin is the most plentiful (about 60% of silymarin) and it is also considered the most active. As part of the Phytosome process silybin is isolated from the other two (Silydianin and Silychristin) for greatest effectiveness. The last part of the image shows how the silybin is bound to phosphatidylcholine on a molecular level to create the active ingredient in Milk Thistle Phytosome. This molecular binding to a substance that is readily absorbed is what increases absorption of silybin in Milk Thistle Phytosome up to ten times more than 80% standardized milk thistle formulas.

Merits of phytosomes

Phytosomes have the following merits(12-14).

- It enhances the absorption of herbal constituent and hence the bioavailability.
- By enhancing the solubility of bile to herbal constituent, facilitates the liver targeting.
- As the absorption of chief phytoconstituent is improved, its dose requirement is also reduced.
- Phosphatidylcholine used in preparation of phytosomes, besides acting as a carrier also acts as a hepatoprotective, hence giving the synergistic effect.
- Unlike liposome, chemical bonds are formed between phosphatidylcholine molecule and phytoconstituent, so the phytosomes show better stability profile.

Hepatoprotective potential

Most of the phytosomal studies are focused to *Silybum marianum* which contains premier liver-protectant flavonoids. The fruit of the milk thistle plant (*S. marianum*, Family Asteraceae) contains flavonoids known for hepatoprotective effects(15,16). Silymarin has been shown to have positive effects in treating liver diseases of various kinds, including hepatitis; cirrhosis; fatty infiltration of the liver (chemical and alcohol induced fatty liver); and inflammation of the bile-duct(17-20). The antioxidant capacity of silymarin substantially boosts the liver's resistance to toxic insults(21). Silymarin primarily contains three flavonoids of the flavonol subclass (having a fully saturated C-ring). Silybin predominates, followed by silydianin and silychristin. Silybin is actually a flavonolignan, probably produced within the plant by the combination of a flavonol with a coniferyl alcohol. It is now known that silybin is the most potent of the three(15). Silybin protects the liver by conserving glutathione in the parenchymal cells(21), while PC helps repair and replace cell membranes(22). These constituents likely offer the synergistic benefit of sparing liver cells from destruction. In its native form within the milk thistle fruit, silybin occurs primarily complexed with sugars, as a flavonyl glycoside or flavonolignan. Silybin has been extensively researched and found to have impressive bioactivity, albeit limited by poor bioavailability.

Yanyu et al (2006) prepared the silymarin phytosome and studied its pharmacokinetics in rats. In the study the bioavailability of silybin in rats was increased remarkably after oral administration of prepared silybin-phospholipid complex due to an impressive improvement of the lipophilic property of silybin-phospholipid complex and improvement of the biological effect of silybin(11).

Tedesco et al (2004) reported silymarin phytosome show better antihepatotoxic activity than silymarin alone and can provide protection against the toxic effects of aflatoxin B1 on performance of broiler chicks(23).

Busby et al. (2002) reported that the use of a silymarin phytosome showed a better fetoprotectant activity from ethanol-induced behavioral deficits than uncomplexed silymarin (24).

Bombardelli *et al.* (1991) reported Silymarin phytosomes, in which Silymarin (A standardized mixture of flavanolignans extracted from the fruits of *S. marianum*) was complexed with phospholipids. Phytosomes showed much higher specific activity and a longer lasting action than the single components, with respect to per cent reduction of odema, inhibition of myeloperoxidase activity, antioxidant and free radical scavenging properties(14).

Morazzoni *et al.* (1992) showed that when silybin was given as Siliphos[R], a silybin-PC phytosome at a dose of 200 mg per kg body weight, the silybin from Siliphos remained elevated at 70 hours following oral dosing, while the silybin given alone barely rose above detectable levels until after 25 hours(25). In another study, the same group of researchers showed that when silybin was given as Siliphos[R], a silybin-PC phytosome at a dose of 200 mg per kg body weight, it was detected in the plasma within minutes, and by one hour its levels had peaked. Its plasma levels remained elevated past the six-hour mark. It was also shown that phytosomal silybin rapidly reaches the liver, traverses the liver cells, and appears in the bile within two hours. The amount of silybin reaching the bile from phytosome dosing is at least 6.5 times greater than that from non-complexed silybin (13% versus 2%, over 24 hours)(26).

Pifferi (1991) studied that unlike silybin orally administered silipide (complex of silybin with PC) shows higher pharmacological activity in animal models of hepatic injury. It was also reported that oral bioavailability and specific organ targeting nature of silipide is much greater than that of silybin administered as a component of silymarin(27).

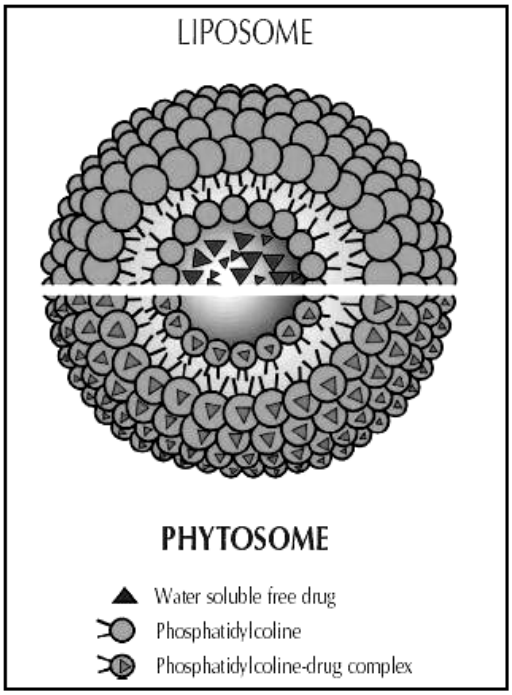
Jiang *et al.* (2002) studied the effects of the Epimedium total Flavonoids Phytosomes (EFP) on preventing and treating bone-loss of the castrate osteoporosis rat model. It was found that using phytosomes improved the bone density, enhanced E_2 level and decreased the IL-6 concentration in serum(28). Jiang *et al.* (2001) optimized the preparation techniques for Herba Epimedii flavonoids phytosomes (EFP). It was found that

PHCOG REV.
An official Publication of Phcog.Net

Table 1: Commercial phytosome preparations(4,43)

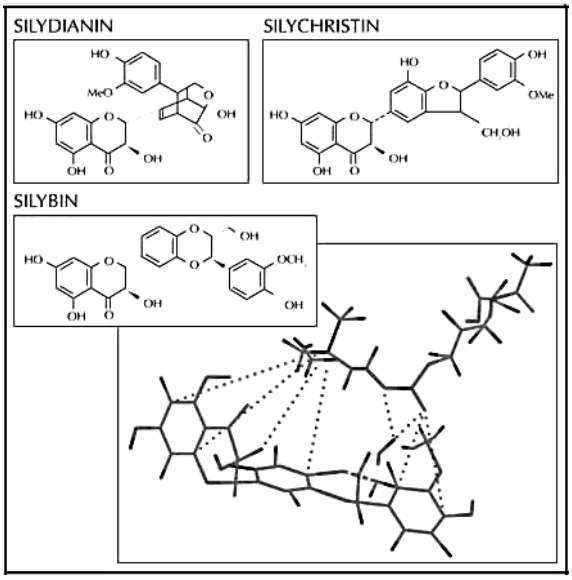
S. No.	Phytosome	Phytoconstituent complexed with phosphatidylcholine	Indication
1.	Silybin Phytosome™	Silybin from Silymarin	Food Product, antioxidant for liver and skin
2.	Ginkgo Phytosome™	24 % ginkgoflavonglycosides from *Ginkgo biloba*	Protects brain and vascular lining ; Anti-skin ageing agent,
3.	Panax Ginseng Phytosome™	37.5 % ginsenosides from roots of *Panax ginseng*	Food Product
4.	Green Tea Phytosome™	epigallocatechin 3-O- gallate from *Camelia sinensis*	Food Product, Systemic antioxidant, Cancer protectant,
5.	Super Milk thistle Extract	Silybin from Silymarin	Food Product; antioxidant for liver and skin
6	Grape seed (PCO) phytosomes	Procyanidolic oligomers (PCOs) from grape seeds	Food Product; protects against heart disease
7.	Hawthorn Phytosomes	Flavonoids	Food Product; In heart disease or hypertension
8.	Centella Phytosome	Terpenes	Vein and Skin disorders

Fig. 1: Major difference between liposome and phytosome



PHCOG REV.
An official Publication of Phcog.Net

Fig. 2: Flavones of Silybum marianum and molecular complexation with phosphatidylcholine



phospholipids effectively enhanced the o/w apparent partition coefficient of icariin by four times and PVP improved the dissolution of phytosomes(29).

Barzaghi *et al.* (1990) studied pharmacokinetic of IdB1016, a silybin-phosphatidylcholine complex in healthy human subjects and concluded that complexation with phosphatidylcholine in IdB 1016 greatly increased the oral bioavailability of silybin by 4.6 times in comparison of simple extract, probably by facilitating its passage across the gastrointestinal mucosa(30).

Buzzelli *et al.* (1993) carried out a pilot study on the liver protective effect of silybin-phosphatidylcholine complex (IdB 1016) in chronic active hepatitis (CAH), and found that IdB 1016 might improve liver function test related to hepatocellular necrosis and/or increased membrane permeability in patients offered by CAH(31).

Carini *et al.* (1992) related 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. It was concluded that IdB 1016 acted as potentially useful protective agent against free radical mediated toxic liver injury(32). 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(33).

Grange *et al.* (1999) conducted a series of studies on silymarin, a standardized extract from the seeds of *S. marianum* (L) Gaertn. administered as the compound Silymarin-Phytosome and found that it could protect the fetus from maternally ingested EtOH(34). Moscarella *et al.* (1993) performed a very small pilot study in which eight patients with chronic active hepatitis (B and/or C) were treated with phytosomal silybin, at 240 mg silybin for two months. Liver enzymes alanine aminotransferase (ALT) and aminotransferase (AST) were significantly reduced, while reductions in glutamyltranspeptidase (GGT) and malondialdehyde (MDA) levels, a byproduct of lipid peroxidation did not attain statistical significance(35).

Marena and Lampertico (1991) studied that healthy volunteers (total number not disclosed) received 360 mg silybin-phytosome complex three times daily for three weeks without adverse effect. They also reported treating 232 patients with "liver disorders" for up to four months with either 240 or 360 mg daily, concluding that the tolerability of the silybin-PC preparation was excellent. Minor adverse effects (nausea, heartburn, dyspepsia, transient headache) were reported in 12 patients (5.2% of the total studied), compared with 8.2 per cent of patients who received non-complexed silybin and 5.1 per cent of patients on placebo. The phytosomal silybin produced no clinically relevant blood changes in these patients. Evaluation of efficacy was based primarily on serum liver enzyme levels, namely aspartate aminotransferase (AST), alanine aminotransferase (ALT), and gamma-glutamyltranspeptidase (GGT)(36).

Comoglio *et al.* (1995) showed that silipide (1:1 complex of silybin with Phosphatidylcholine) has the ability to scavenge ethanol derived free radicals along with antioxidant activity, hence it was concluded that this drug might be potentially useful in counteracting free radical mediated injury involved in the development of liver damage caused by alcohol abuse(37). Other research confirms silybin in silipide can actually trap free radicals within the membranes of liver cells, as such reactive molecular fragments are being generated from carbon tetrachloride and methylhydrazine(38).

Conti *et al.* (1992) tested IdB1016 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 CCl_4, praseodymium, ethanol and galactosamine. Unlike the silybin and

Phosphatidylcholine, in the same dose the complex IdB1016 showed protective activity against paracetamol induced hepatotoxicity(39).

Studies revealed that Silymarin Phytosome containing all three flavonoids of silymarin and with the 2:1 ratio of phosphatidylcholine to silymarin (Milk Thistle Phytosome) is less potent than the preparation (SILIPHOST) containing only silybin (the most potent bioflavonoid of silymarin) in a one to one ratio with phosphatidylcholine. One 150 mg capsule of Milk Thistle Phytosome was found to be slightly less potent than the 120 mg capsule of SILIPHOST(40).

In 1990, Malandrino *et al.* succeeded in improving the bioavailability of silymarin extract by complexing it with soy PC-a phytosome(41). Subsequently, a more purified silybin was complexed with PC. The intermolecular bonding of silybin with PC proved to be specific and stable, and the resulting molecular complex is more soluble in lipophilic, organic solvents(42). This property predicts the enhanced ability of phytosomes to cross cell membranes and enter cells. A major pharma giant Indena S.P.A. Milan, Italy (www.indena.com) has developed the phytosome technology and a series of phytosome preparations of herbal drugs. Some of the commercially available phytosomes are summarized in Table 1.

As confirmed for rats, in the human subjects silybin coming from phytosomes does reach the intended target organ, the liver. This was proven using nine volunteer patients who had earlier undergone surgical gall bladder removal necessitated by gallstones(44,45). They were given single oral doses of 120 mg silybin as silybin phytosome (Siliphos) or silymarin, and bile was monitored for silybin levels. Silybin appeared in the bile and peaked after four hours. In the case of phytosomal silybin, the total amount recovered in the bile after 48 hours accounted for 11 per cent of the total dose. In the case of silymarin, approximately three per cent of the silybin was recovered. These data suggest a four-times greater passage through the liver for phytosomal silybin.

In a study role of phytosome in the treatment of non alcoholic fatty liver disease (NAFLD) was reviewed. Silybin is the main component of silymarin that is absorbed when linked with a phytosome. This substance reduces in rats the lipid-peroxidation and the activaction of hepatic stellate cells. In humans, some non controlled data show that silybin is able to reduce insulin resistance, liver steatosis and plasma markers of liver fibrosis(46).

In 1992, researchers at the Universities of Milan and Bari reported on a controlled study of chronic persistent hepatitis(47). The study recruited only patients with biopsy-confirmed hepatitis. The drug treatments available for this condition have limited efficacy, do not work at all for many patients, and have major adverse effects. These patients were randomized to receive either 240 mg silybin phytosome (n=31) or placebo (n=34), one capsule orally, twice daily for three months. The phytosome group experienced significant lowering of both serum ALT and AST, while in the placebo group both enzyme indicators worsened. The silybin treatment was well tolerated, with even fewer adverse events reported than for the placebo group, and no patient discontinued the trial due to adverse effects.

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(48). Recently Maiti *et al.* (2006) developed the phytosomes of curcumin and naringenin in two different studies (9,10). In the first study phytosome of curcumin was developed to overcome the limitation of absorption and to investigate the protective effect of curcumin–phospholipid complex on carbon tetrachloride induced acute liver damage in rats. The complex showed enhanced aqueous or *n*- octanol solubility. The antioxidant activity of the complex was significantly higher than pure curcumin in all dose levels tested. In the other study the developed phytosome of naringenin produced better antioxidant activity than the free compound with a prolonged duration of action, which may be helpful in reducing the fast elimination of the molecule from body.

Semalty *et al.* reviewed the role of phytosome in herbal drug delivery and isolated polyphenolic phytoconstituents (flavonoids, xanthones etc.) from various medicinal plants of Garhwal Himalayan region for development of their phytosomes for hepatoprotective activity(49,50). Recently Mukherjee *et al.* has also reviewed Phytosomes as a value added herbal drug delivery system(51).

CONCLUSION

Polyphenolic polar phytoconstituents, when complexed with phospholipids like phosphatidylcholine give rise to a new delivery system called Phytosome. Phytosomes show definite physicochemical and spectroscopic characteristics. Like liposomes, phytosomes products show their potential in cosmetics as anti-skin ageing agents and for the use of other nonpathogenic skin conditions. But the phytosomes are superior to liposomes due to much better absorption and stability profile.

Phytosome can also play a vital role in efficient herbal drug delivery of a broad spectrum of hepatoprotective phytoconstituents like flavones, xanthones, terpenes etc. After screening and selection of potential phytoconstituents from medicinal plants, phytosomes can be developed for various therapeutic uses like cardiovascular, anti-inflammatory and anticancer activities etc.

ACKNOWLEDGMENTS

Authors acknowledge the grant provided by the Department of Science & Technology, Govt. of India for the research work. Authors are also thankful to LIPOID GmbH Germany for providing the gift sample of phosphatidylcholine for the research work.

REFERENCES

1. C. Manach, A. Scalbert, C. Morand. Polyphenols: food sources and bioavailability, Am. J. Clin. Nutr. 79:727-47 (2004).
2. E. Bombardelli, S.B. Curri, R. Loggia Della, N. P. Del, A. Tubaro, P.Gariboldi. Complexes between phospholipids and vegetal derivatives of biological interest. Fitoterapia. 60:1-9 (1989).
3. U. Citernesi and M. Sciacchitano. Phospholipids/active ingredient complexes. Cosm & Toil. 110(11): 57-68 (1995)
4. Murray. Phytosomes- Increase the absorption of herbal extract, Available at: www.doctormurray.com/articles/silybin.htm. Accessed- January 18, 2006,

5. E. Bombardelli. Phytosome: new cosmetic delivery system. Boll Chim Farm.130(11): 431-38 (1991)
6. E. Bombardelli and M. Spelta. Phospholipid-polyphenol complexes: A new concept in skin care ingredients. Cosm & Toil. 106(3): 69-76 (1991).
7. C. Marena, M. Lampertico. Preliminary clinical development of silipide: a new complex of silybin in toxic liver disorders. Planta Med. 57:A 124-25 (1991).
8. Y.N. Jiang, Z.P. Yu, Z.M. Yan and J.M. Chen. Studies on preparation of herba epimedii flavanoid phytosomes and their pharmaceutics. Zhongguo Zhong Yao Za Zhi., 26(2): 105-8 (2001)
9. K. Maiti, K. Mukherjee, A. Gantait, B.P. Saha, P.K. Mukherjee. Curcumin-phospholipid complex: Preparation, therapeutic evaluation and pharmacokinetic study in rats. Int. J. pharm. Sept. 2006 (In Press)
10. K. Maiti, K. Mukherjee, A. Gantait, B.P. Saha, P.K. Mukherjee. Enhanced therapeutic potential of naringenin-phospholipid complex in rats. J Pharm Pharmacol. 58(9):1227-33 (2006).
11. X. Yanyu, S. Yunmei, C. Zhipeng, P. Quineng. The preparation of silybin-phospholipid complex and the study on its pharmacokinetics in rats. Int J Pharm. 3;307(1):77-82 (2006).
12. P. Kidd and K. Head. A review of the bioavailability and clinical efficacy of milk thistle Phytosome: a silybin-phosphatidylcholine complex. Altern. Med. Rev. 10(3):193-203 (2005).
13. E. Bombardelli. Phytosomes in functional cosmetics. Fitoterapia., 65(5): 320-27 (1994)
14. E. Bombardelli, M. Spelta, R. Loggia Della, S. Sosa, A. Tubaro. Aging Skin: Protective effect of silymarin- PHYTOSOME. Fitoterapia. 62(2): 115-22 (1991).
15. H. Hikino, Y. Kiso, H. Wagner, M. Fiebig. Antihepatotoxic actions of flavonolignans from *Silybum marianum* fruits. Planta Med. 50:248-250 (1984),
16. K. Wellington, B. Jarvis. Silymarin: a review of its clinical properties in the management of hepatic disorders. BioDrugs. 15: 465-89 (2001).
17. F. Canini, Bartolucci, E. Cristallini. Use of silymarin in the treatment of alcoholic hepatic steatosis. Clin Ter.114:307-14 (1985).
18. H.A. Salmi and S. Sarna. Effect of silymarin on chemical, functional, and morphological alteration of the liver. A double-blind controlled study. Scand. J. Gastroenterol. 17:417-21 (1982).
19. C. Boari, F.M. Montanari, G.P. Galletti. Occupational toxic liver diseases. Therapeutic effects of silymarin. Minerva Med. 72:2679-88 (1981)
20. P. Ferenci, B. Dragosics, H. Dittrich. Randomized controlled trial of silymarin treatment in patients with cirrhosis of the liver. J. Hepatol. 9:105-13 (1989).
21. A. Valenzuela, M. Aspillaga, S. Vial, R. Guerra. Selectivity of silymarin on the increase of the glutathione content in different tissues of the rat. Planta Med. 55:420-22 (1989)
22. P.M. Kidd. Phosphatidylcholine: a superior protectant against liver disease. Altern. Med. Rev. 1:258-74 (1996).
23. D. Tedesco, S. Steidler , S. Galletti , M. Tameni , O. Sonzogni , L. Ravarotto. Efficacy of silymarin-phospholipid complex in reducing the toxicity of aflatoxin B1 in broiler chicks. Poult Sci. 83(11):1839-43 (2004).
24. A. Busby, L. La Grange, J. Edwards, J. Kings. The use of a silymarin/phospholipid compound as a fetoprotectant from ethanol-induced behavioral deficits. J Herb Pharmacother. 2(1):39-47 (2002)
25. P. Morazzoni, M.J. Magistretti, C. Giachetti, G. Zanolo. Comparative bioavailability of Silipide, a new flavanolignan complex, in rats. Eur. J. Drug Metab. Pharmacokinet., 17:39-44 (1992).
26. P. Morazzoni, A. Montalbetti, S. Malandrino, G. Pifferi. Comparative pharmacokinetics of silipide and silymarin in rats. Eur. J. Drug Metab. Pharmacokinet. 18:289-97 (1993).
27. G. Pifferi. Silipide: a new bioavailabe complex of silybin. Planta Medica. 57 (2): A12 (1991).
28. Y. N. Jiang, H. Y. Mo and J.M. Chen. Effects of the epimedium total flavonoids phytosomes on preventing and treating bone-loss of ovariectomized rats. Zhongguo Zhong Yao Za Zhi, 27(3):221-4 (2002)
29. Y.N. Jiang, Z.P. Yu, Z..M. Yan. and J.M. Chen. Studies on preparation of herba epimedii flavanoid phytosomes and their pharmaceutics. Zhongguo Zhong Yao Za Zhi. 26(2): 105-8. (2001)
30. N. Barzaghi, F. Crema, G. Gatti, G. Pifferi and E. Perucca. Pharmacokinetic studies on IdB 1016, a silybin phosphatidylcholine complex in healthy human subjects. Eur. J. Drug Metab. Pharmacokinet. 15:333-38 (1990).
31. G. Buzzelli, S. Moscarella, A. Giusti, A. Duchini, C. Marena and M. Lampertico. A pilot study on the liver protective effect of silybinphosphatidylcholine complex (IdB 1016) in chronic active hepatitis. Int. J. Clin. Pharmacol. Ther. Toxicol. 31:456-60 (1993).
32. R. Carini, A. Comoglio, E. Albano, G. Poli. Lipid peroxidation and irreversible damage in the rat hepatocyte model. Protection by the silybinphospholipid complex IdB 1016. Biochem Pharmacol. 43:2111-15 (1992).
33. A. Vailati, L. Aristia, E. Sozze, F. Milan, V. Inglese, P. Calenda, P.A. Bosollo. Randomized open study of the dose-effect relationship of a short course of IdB 1016 in patients with viral or alcoholic hepatitis. Fitoterapia. 64:219-228 (1993).
34. L. La. Grange, M. Wang, R. Watkins, D. Ortiz, M.E. Sanchez, J. Konst, C. Lee and E. Reyes. Protective effects of the flavonoids mixture, silymarin, on fetal rat brain and liver. J. Ethnopharm., 65: 53-61 (1999).
35. Moscarella S., Giusti A., Marra F., Marena C., Lampertico M., Relli P., Gentilini P., Buzzelli G., Therapeutic and antilipoperoxidant effects of silybin phosphatidylcholine complex in chronic liver disease: preliminary results, Curr. Ther. Res., 53:98-102 (1993).
36. C. Marena, M. Lampertico. Preliminary clinical development of silipide: a new complex of silybin in toxic liver disorders. Planta Med., 57:A 124-A125 (1991).
37. A. Comoglio, A. Tomasi, S. Malandrino, G. Poli and E. Albano. Scavenging effect of silipide, a new silybinphospholipid complex, on ethanol-derived free radicals. Biochem Pharmacol. 50:1313-16(1995).
38. A. Comoglio, G. Leonarduzzi, R. Carini, D. Busolin, H. Basaga, E. Alabano, A. Tomasi, G. Poli, P. Morazzoni, M.J. Magistretti. Studies on the antioxidant and free radical scavenging properties of IdB 1016 a new flavanolignan complex. Free Radic. Res. Commun. 11:109-15 (1990).
39. M. Conti, S. Malandrino, M.J. Magistretti. Protective activity of silipide on liver damage in rodents. Jpn. J. Pharmacol. 60:315-21(1992).
40. Murray, SILIPHOST: Nature's Potent Liver Remedy, Available at: http://www.doctormurray.com/articles/silybin.htm. Accessed -February 15, 2006
41. S. Malandrino, G. Pifferi, IdB-1016. Drugs Future; 1990, 15:226-227.
42. B. Gabetta, G.F. Zini, G. Pifferi. Spectroscopic studies on IdB 1016, a new flavanolignan complex. Planta Med. 55:615 (1989).
43. Vitamedics, Phytosome Products, Available at http://www.vitamedics.com. Accessed - February 15, 2006 ,
44. R. Schandalik, G. Gatti, E. Perucca. Pharmacokinetics of silybin in bile following administration of silipide and silymarin in cholecystectomy patients. Arzneimittelforschung. 42:964-68 (1992).
45. R. Schandalik, E. Perucca. Pharmacokinetics of silybin following oral administration of silipide in patients with extrahepatic biliary obstruction. Drugs Exp. Clin. Res. 20:37-42 (1994).
46. M. Trappoliere, C. Tuccillo, A. Federico, A. Di Leva, M. Niosi, C. D'Alessio, R. Capasso, F. Coppola, M. Dauria, C. Loguercio. The treatment of NAFLD. Eur Rev Med Pharmacol Sci. Sep-Oct;9(5):299-304 (2005).
47. R. Marcelli, P. Bizzoni, D. Conte. Randomized controlled study of the efficacy and tolerability of a short course of IdB 1016 in the treatment of chronic persistent hepatitis. Eur Bull Drug Res. 1:131-135 (1992).
48. K. Maiti, K. Mukherjee, A. Gantait, H.N. Ahamed, B.P. Saha, P.K. Mukherjee. Enhanced therapeutic benefit of quercetin–phospholipid complex in carbon tetrachloride induced acute liver injury in rats: a comparative study. Iran J. Pharmacol. Ther. 4: 84–90(2005).
49. A. Semalty, Mona Semalty, R. Singh, M.S.M. Rawat, S. K Saraf, Shubhini Saraf, Phytosome: the phyto-phospholipid complexes in improving bioavailability of herbal drugs. J. Herbal Pharacother. Accepted (2007).
50. A. Semalty, Mona Semalty, S. K Saraf, Shubhini Saraf, Phytosome: A New Herbal Drug Delivery System. In: V.K.Singh, J.N. Govil, C. Arunachalam, eds. Recent Progress in Medicinal Plants Vol 19, LLC Newyork, Studium Press; 223-36 (2007).
51. P.K. Mukherjee, K. Maiti, V. Kumar. Value added drug delivery systems with botanicals: Approach for Dosage development from natural resources. Pharma Rev. 6: 57-60 (2007).