International Journal of Research and Development in Pharmacy and Life Sciences
Available online at http//www.ijrdpl.com
August - September, 2012, Vol. 1, No.3, pp 143-150
ISSN: 2278-0238

Review Article

PHYTOSOMAL DRUG DELIVERY SYSTEMS

Rawat Swati *[1] and Motwani Sapna [2]

1. SND College of Pharmacy, Yeola, Nashik, (Maharashtra) - India.
2. Modern College of Pharmacy, Indore (M.P.), 452001

***Corresponding Author: Email** swatimonalisa @rediffmail.com

(Received: May 14, 2012, 2011; **Accepted:** July 19, 2012**)**

ABSTRACT

Certain of the water-soluble flavonoid molecules can be converted into lipid-compatible molecular complexes, aptly called phytosomes. Phytosomes are better able to transition from a hydrophilic environment into the lipid-friendly environment of the outer cell membrane, and from there into the cell, finally reaching the blood. The term "phyto" means plant while "some" means cell-like. Phytosome is a complex of a natural active ingredient and a phospholipid. It is claimed that phytosome increases absorption of "conventional herbal extracts" or isolated active principles. The phytosome process is that combines herbal extracts and soybean phospholipids (lecithin). phytosomes are created when the standardized extract and active ingredients of a herb are bound to the phospholipids on a molecular level. The newly created Phytosome structures contain the active ingredients of the herb surrounded by the phospholipids. The phospholipid molecular structure includes a water-soluble head and two fat-soluble tails. Because of this dual solubility, the phospholipid acts as an effective emulsifier. The newly created phytosome structures contain the active ingredients of the herb surrounded by the phospholipids. The phospholipid molecular structure includes a water-soluble head and two fat-soluble tails. Because of this dual solubility, the phospholipid acts as an effective emulsifier. An emulsifier is a material that can combine two liquids that normally will not mix well together. By combining the emulsifying action of the phospholipids with the standardized botanical extracts, the phytosome form provides dramatically enhanced bioavailability and delivers faster and improved absorption of the active constituents of the herb in the intestinal tract.

Keywords: Phytosome, phosphatidylcholine, herbal extracts, phytomedicines.

INTRODUCTION

Preparations of plants or parts of them were widely used in popular medicine since ancient times and till today the use of phytomedicines is widespread in most of the world's population. During the last century chemical and pharmacological studies have been performed on a lot of plant extracts in order to know their chemical composition and confirm the indications of traditional medicine. It has often been observed that the separation and purification of the various components of an extract may lead to a partial loss of specific activity for the purified component; this is probably due to the removal of chemically related substances contributing with a synergic action to the activity of the main components[1]. Very often the chemical complexity of the extract seems to be essential for the bioavailability of the active components. Some active components might interact with other molecules present in the extract with formation of complexes.

Phytosomes are advanced forms of herbal products that are better absorbed, utilized, and as a result produce better results than conventional herbal extracts. Phytosomes are produced via a patented process whereby the individual components of an herbal extract are bound to phosphatidylcholine - an emulsifying compound derived from soy.[2-3] Phosphatidylcholine is also one of the chief components of the membranes in our cells.

Most of the bioactive constituents of phytomedicines are flavonoids (e.g., anthocyanidins from bilberry, catechins from green tea, silymarin from milk thistle). However, many flavonoids are poorly absorbed. The poor absorption of flavonoid nutrients is likely due to two factors. First, they are multiple-ring molecules too large to be absorbed by simple diffusion, while they are not absorbed actively, as occurs with some vitamins and minerals. Second, flavonoid molecules typically have 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[4].

Water-soluble flavonoid molecules can be converted into lipid-compatible molecular complexes, aptly called phytosomes. Phytosomes are better able to transition from a hydrophilic environment into the lipid-friendly environment of the enterocyte cell membrane and from there into the cell, finally reaching the blood. The lipid-phase substances employed to make flavonoids 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 when taken by mouth. Precise chemical analysis indicates a phytosome is usually a flavonoid molecule linked with at least one PC molecule. A bond is formed between the two molecules, creating a hybrid molecule. This highly lipid-miscible hybrid bond is better suited to merge into the lipid phase of the enterocyte's outer cell membrane.[5-6]

Phosphatidylcholine is not merely a passive "carrier" for the bioactive flavonoids of the phytosomes, but is itself a bioactive nutrient with documented clinical efficacy for liver disease, including alcoholic hepatic steatosis, drug-induced liver damage, and hepatitis. The intakes of phytosome preparations sufficient to provide reliable clinical benefit often also provide substantial PC intakes.[7] Phytosomes are not liposomes; structurally, the two are distinctly different. The phytosome is a unit of several molecules bonded together, while the liposome is an aggregate of many phospholipid molecules that can enclose active phytomolecules, but without specifically bonding to them.[8]

PROPERTIES OF PHYTOSOMES

Phytosome is a complex between a natural product and natural phospholipids, like soy phospholipids. Such a complex is obtained by reaction of stoichiometric amounts of phospholipid and the substrate in an appropriate solvent. On the basis of spectroscopic data it has been shown that the main phospholipid-substrate interaction is due to the formation of hydrogen bonds between the polar head of phospholipids (i.e. phosphate and ammonium groups) and the polar functionalities of the substrate. When treated with water, Phytosome assumes a micellar shape forming liposomal-like structures, but while in liposomes the active principle is dissolved in the internal pocket or it is floating in the layer membrane, in phytosome the active principle is anchored to the polar head of phospholipids, becoming an integral part of the membrane. In the case of the catechindistearoylphosphatidylcholine complex, for example, there is the formation of H-bonds between the phenolic hydroxyls of the flavone moiety and the phosphate ion on the phosphatidylcholine side. This can be deduced from the comparison of the NMR of the complex with those of the pure precursors. The signals of the fatty chain are almost unchanged. Such evidences inferred that the two long aliphatic chains are wrapped around the active principle, producing a lipophilic envelope which shields the polar head of the phospholipids and the catechins. Additional evidences of the phytosome structure are obtained applying the solid state NMR technique. Proton relaxation studies, by means of spin diffusion process, show that the phytosome are not mechanical mixture but a complex due to dipolar interactions between the two constituents. This can be confirmed by IR spectroscopy, comparing the spectrum of the complex to the one of the individual components and their mechanical mixture. The particular structure of phytosome elicits peculiar properties and advantages in cosmetic application. Phytosome retain the solubility in fats and in lipophylic media of the precursor phospholipid. Furthermore they act as a carrier of the active principle through lipophilic membranes.

Their low solubility in aqueous media allows the formation of stable emulsions or creams.[9-12]

The increased bioavailability of the phytosome over the non complexed botanical derivatives has been demonstrated by pharmacokinetics studies or by pharmacodynamic tests in experimental animals and in human subjects. The similar things have been studied in some marketed products.

LEUCOSELECT®[13] is composed of oligomeric polyphenols (grape procyanidins) complexed with soy phospholipids. This results in a markedly improved oral bioavailability of procyanidins, which are widely recognized to exert a protective activity on the cardiovascular system through an integrated network of specific mechanisms of action including a unique antioxidant effect. It is composed of oligomeric polyphenols (grapeprocyanidins) of varying molecular size, complexed with phospholipids. The markedly improved oral bioavailability of these procyanidins flavonoids offers marked protection for the cardiovascular system and other organs through a network of mechanisms that extend beyond their great antioxidant potency.

GINKGOSELECT®[14] is an easy absorbable form of the standardized extract of *Ginkgo biloba* leaves. Its major indications are cerebral insufficiency and peripheral vascular disorders, and it is an appropriate aid in situations of reduced cerebral performance. Its better oral bioavailability and the good tolerability make it the ideal product even for long term treatments. It is a more fully absorbable form of the standardized extract of Ginkgo biloba leaves. Its major indications are cerebral insufficiency and peripheral vascular disorders, and it also can ameliorate reduced cerebral circulation. Its improved oral bioavailability and good tolerability makes it the ideal Ginkgo product even for long term treatment.

GREENSELECT®[15] contains a totally standardized polyphenolic fraction (not less than 66.5%) obtained from green tea leaves and mainly characterized by the presence of epigallocatechin and its derivatives. These compounds are demostrated to be strong *in vitro* modulators of several biochemical processes mainly involved in the pathogenesis of major chronic-degenerative diseases such as cancer and atherosclerosis. The complexation of green tea polyphenols with phospholipids strongly improves their low and erratic oral bioavailability. It contains a totally standardized polyphenolic fraction (not less than 66.5 percent) obtained from green tea leaves and mainly characterized by the presence of epigallocatechin and its derivatives. These compounds are potent modulators of several biochemical processes linked to the breakdown of homeostasis in major chronic-degenerative diseases such as cancer and atherosclerosis. The complexation of green tea polyphenols with phospholipids strongly improves their poor oral bioavailability.

SILIPHOS®[16] prevents liver damage of different etiology. SILIPHOS® is the most absorbable form of silybin known up to now, as it allows silybin to reach the target organ, the liver, in concentrations which are reported to be effective as antihepatotoxic.

MIRTOSELECT®[17] contains an extract of bilberry which provides anthocyanosides. These improve capillary tone, reduce abnormal blood vessel permeability, and are potent antioxidants. They hold great potential for the management of retinal blood vessel problems and venous insufficiency.

SABALSELECT®[18] includes an extract prepared from saw palmetto berries through supercritical CO2 (carbon dioxide) extraction. It delivers fatty acids, alcohols and sterols that benefit prostate health. In particular this extract may benefit non-cancerous prostate enlargement.

LYMPHASELECT™[19] includes a standardized extract from Melilotus officinalis. This preparation is particularly indicated for venous disorders, including chronic venous insufficiency of the lower limbs.

OLEASELECT ™ is a newer preparation from olive oil polyphenols. These are potent free radical scavengers (antioxidants), inhibit harmful oxidation of LDL cholesterol, and also have anti-inflammatory activity.

POLINACEA ™ is an immunomodulating preparation made from Echinacea angustifolia. It includes echinacosides and a unique high-molecular weight polysaccharide. This preparation especially enhances immune function in response to a toxic challenge. For all these breakthrough phytomedicines, the PHYTOSOME technology enables cost effective delivery AND synergistic benefits from the phospholipid nutraceuticals intrinsic to life.[20-22]

HERBAL CONSTITUENTS USED IN PHYTOSOMAL DRUG DELIVERY

Flavonoids

Plants are endowed with myriad health giving substances, prominent among these being the flavonoids. First recognized for their antioxidant properties, flavonoids are widely distributed in food and medicinal plants. To date, more than 4,000 naturally occurring flavonoids have been identified, each with its own distinctive molecular structure and 3-D shape. Flavonoids are part of a broader class of dietary antioxidants called polyphenols (literally, having more than one phenolic ring). The flavonoids are distinctive for their triple ring structures. Subclasses of the flavonoids exist, classified mostly on the degree of oxidation of the oxygen heterocycle or C-ring. Molecular 3-D shape or "configuration" is an important aspect of flavonoid biology. Individual flavonoids have been found to specifically protect vulnerable molecular sites on cells, to stimulate or inhibit the active sites. The unit phytosome is PC linked to the flavonoid molecule (lower right). From Bombardelli et al. of enzymes and receptors, or to exert other shape - specific molecular actions. Among foodstuffs, the flavonoids are most abundant in berries and other fruits, a few vegetables, and in cocoa and tea beverages.[23] as a rule, the flavonoids are poorly absorbed from foods - for greater than 10% of the administered dose to reach the blood is the rare exception. Epidemiological evidence suggests that the lower intakes of flavonoids are associated with heightened risk of cardiovascular disease, but is not yet conclusive A very active area of current research is focused on flavonoids that down-regulate receptors for prostaglandins, cytokines, or hormones on cancerous or other abnormal cells. Molecular configuration may prove to be just as important as antioxidant action in the diverse anti - inflammatory, anti-allergic, antiviral, anticancer, and immune-stimulant applications of flavonoids. Then by taking flavonoid preparations with the greatest health giving potential and making them into phytosomal preparations, Indena scientists achieved a breakthrough in phytomedicine.[24]

Terpenoids: Natural products and related compounds formally derived from isoprene units (Fig. 2). They contain oxygen in various functional groups. This class is subdivided according to the number of carbon atoms in the same manner as are *terpenes*. The skeleton of terpenoid may differ from strict additivity of isoprene units by the loss or shift of a fragment, generally a methyl group.[25]

Carotenoids: This class includes *carotenes*, *xanthophylls* and certain compounds that arise from rearrangement of the skeleton of (I) or by loss of part of this structure. *Retinoids* are excluded.[26]

Isoprenoids: Compounds formally derived from isoprene (2-methylbuta-1,3-diene), the skeleton of which can generally be discerned in repeated occurrence in the molecule. The skeleton of isoprenoids may differ from strict additivity of isoprene units by loss or shift of a fragment, commonly a methyl group. The class includes both *hydrocarbon* and oxygenated derivatives.

Terpenes: Hydrocarbons of biological origin having carbon skeletons formally derived from isoprene [$CH_2=C(CH_3)CH=CH_2$]. This class is subdivided into the C_5 hemiterpenes, C_{10} monoterpenes, C_{15} sesquiterpenes, C_{20} diterpenes, C_{25} sesterterpenes, C_{30} triterpenes, C_{40} tetraterpenes (carotenoids), and C_{5n} polyterpenes. Fig.3 shows typical Phytosomal phase arrangement. The lipid - phase substances that successfully employed to make flavonoids lipid compatible are phospholipids from soy, mainly phosphatidylcholine (PC). PC is miscible both in the water phase and in oil/lipid phases, and is excellently absorbed when taken by mouth. PC is the principal molecular building block for cell membranes (Fig. 4), and the molecular properties that suit PC for this role also render it close to ideal for its PHYTOSOME® role.

Precise chemical analysis indicates the unit phytosome is usually a flavonoid molecule linked with at least one PC molecule. A bond is formed between the two molecules to create a hybrid molecule; this hybrid is highly lipid - miscible, better suited to merge into the lipid phase of the enterocyte's outer cell membrane

PHYTOSOMES ARE NOT LIPOSOMES

Phytosomes are not liposomes - structurally, the two are distinctly different as shown in Fig. The phytosome is a unit of a few molecules bonded together, while the liposome is an aggregate of many phospholipid molecules that can enclose other phytoactive molecules but without specifically bonding to them. Liposomes are touted delivery vehicles, but for dietary supplements their promise has not been fulfilled. But

for Indena's phytosome products numerous studies prove they are markedly better absorbed and have substantially greater clinical efficacy.[9-10] Indena has successfully applied this technology to a number of standardized flavonoid preparations.

Liposomes are used primarily in cosmetics to deliver water-soluble substances to the skin. A liposome is formed by mixing a water-soluble substance with phosphatidylcholine. No chemical bond is formed; the phosphatidylcholine molecules collectively surround the water-soluble substance. There may be hundreds or even thousands of phosphatidylcholine molecules surrounding the water-soluble compound. In contrast, with the Phytosome process the phosphatidylcholine and the individual plant components actually from a 1:1 or a 2:1 complex depending on the substance. This difference results in Phytosomes being much better absorbed that liposomes. Not surprisingly, Phytosomes are also superior to liposomes in skin care products. The PHYTOSOME® technology is a breakthrough model for:

• Marked enhancement of bioavailability
• Significantly greater clinical benefit
• Assured delivery to the tissues
• No compromise of nutrient safety

Is there scientific documentation to support the claims of superiority of Phytosomes?

Yes, there is a growing body of scientific studies showing improved absorption, utilization, and results with the Phytosome process. SILYBIN PHYTOSOME™[27-28] is the well-studied. Silybin is the chief component of silymarin, the flavonoid complex from milk thistle valued for its ability to protect and restore the liver. Silybin is the most potent of these active substances. What the research has shown in both human and animal studies is that SILYBIN PHYTOSOME™ is better absorbed compared to an equal amount of silybin in conventional milk thistle extracts. In one human study, the excretion of silybin in the bile was evaluated in patients undergoing gallbladder removal for gallstones. A special drainage tube, the T-tube, was used to get the samples of bile necessary. Patients were given either a single oral dose of the SILYBIN PHYTOSOME™ or milk thistle extract (80% silymarin). The amount of silybin recovered in the bile within 48 hours was 11% for the SILYBIN PHYTOSOME™ group and 3% for silymarin group.[29-30] One of the significant features of this study is the fact that silybin has been shown to improve the solubility of the bile. Since more silybin is being delivered to the liver and gallbladder when the SILYBIN PHYTOSOME™ is used, this form is the ideal form for individuals with gallstones or fatty-infiltration of the liver – two conditions characterized by decreased bile solubility. In another human study designed to assess the absorption of silybin when directly bound to phosphatidylcholine, plasma silybin levels were determined after administration of single oral doses of SILYBIN PHYTOSOME™ and a similar amount of silybin from milk thistle extract in healthy volunteers. The results indicate that the absorption of silybin from SILYBIN PHYTOSOME™ is approximately 7 times greater compared to the absorption of silybin from regular milk thistle extract (70-80% silymarin content). Similar results have been noted in studies comparing Green Tea Phytosome with green tea extract looking at the blood levels of the key compound epigallocatechin 3-O- gallate.[31-33]

Phytomedicines, complex chemical mixtures prepared from plants, have been used in medicine since ancient times and continue to have widespread popular use. PHYTOSOME dietary supplements are the modern culmination of this great tradition. PHYTOSOME is a patented process developed by Indena, a leading supplier of nutraceutical ingredients, to incorporate phospholipids into standardized extracts and so vastly improve their absorption and utilization. Over the past century, chemical and pharmacologic science established the compositions, biological activities and health giving benefits of numerous plant extracts. But often when individual components were separated from the whole there was loss of activity—the natural ingredient synergy became lost. Standardization was developed to solve this problem.[34-35]

As standardized extracts became established, poor bioavailability often limited their clinical utility. Then it was discovered that complexation with certain other clinically useful nutrients substantially improved the bioavailability of such extracts. The nutrients so helpful for enhancing the absorption of other nutrients are the phospholipids.[36] Phospholipids are complex molecules that are used in all known life forms to make cell membranes. They are cell membrane building blocks, making up the matrix into which fit a large variety of proteins that are enzymes, transport proteins, receptors, and other biological energy converters.

In humans and other higher animals the phospholipids are also employed as natural digestive aids and as carriers for both fat-miscible and water miscible nutrients. Increased bioavailability of the PHYTOSOMES over the simpler, noncomplexed plant extracts has been demonstrated by pharmacokinetic (tissue distribution) and activity studies, conducted in animals as well as in humans. PHYTOSOME has an added dimension: the proven health giving activity of the phospholipids themselves.[37-39]

ADVANTAGES AND APPLICATIONS

1. Better bioavailability (Silybin Phytosomes): There is a growing body of scientific studies showing improved absorption, utilization, and results with the Phytosome process. SILIPHOST (Silybin Phytosome) is the well-studied. Silybin is the chief component of silymarin, the flavonoid complex from milk thistle valued for its ability to protect and restore the liver. Silybin is the most potent of these active substances. SILIPHOST contains one part silybin to one part phosphatidylcholine while Milk Thistle Phytosome is a less potent version as it contains all three flavonoids of silymarin and the ratio of to phosphatidylcholine to silymarin is 2:1. The research has shown in both human and animal studies is that SILIPHOST is better absorbed compared to an equal amount of silybin in conventional milk thistle extracts[38-42].

2. Antitumor activity of the silybin-phosphatidylcholine complex, IdB 1016, against human ovarian cancer was studied. This study aimed to assess, in an in vivo experimental model, the growth inhibitory effects of IdB 1016 (Silipide, a complex of silybin/phosphatidylcholine) when used as a single agent against human ovarian cancer.

3. New effects and applications of Silybin and silymarin -: The polyphenolic fraction from the seeds of *Silybum Marianum* and its main component silybin. Silymarin and silybin were studied as hepatoprotectants shown to have other interesting activities as e.g., anticancer and canceroprotective. These activities were demonstrated in a large variety of illnesses of different organs as e.g., prostate, lungs, CNS, kidneys, pancreas and others. Besides the cytoprotective activity of silybin mediated by its antioxidative and radical-scavenging properties also new activities based on the specific receptor interaction were discovered - e.g., inhibition and modulation of drug transporters, P-glycoproteins, estrogenic receptors, nuclear receptors and some others. New derivatives of silybin open new ways to its therapeutic applications. Pharmacology dealing with optically pure silybin diastereomers may suggest new mechanisms of its action.

4. Vessel maturation effects on tumor growth: In an experiment, [39] Validation of a computer model in implanted human ovarian carcinoma spheroids. Measurements of tumor growth, neovascular maturation and function in human epithelial ovarian carcinoma xenografts were performed. Results suggest that vascular maturation and mature and immature vessel regression occur continuously during tumor neovascularisation. Moreover, in these spheroids, a high tumor growth-rate is associated with monotonic changes in vessel density (VD) and with large proportions of mature blood vessels, whereas a lower tumor growth-rate is associated with fluctuating VD and lower proportions of mature vessels. These results corroborated a mathematical model for tumor dynamics, including vascular maturation and immature and mature vessel regression.

6. Peritoneal dissemination of ovarian cancer and tumor angiogenesis was studied in Pyrrolo[2,1-c][1,4]benzodiazepine dimer SJG-136 (NSC 694501) selectively cross-links guanine residues located on opposite strands of DNA, and found to exhibit potent in vitro cytotoxicity. In addition, SJG-136 was highly active in vivo in hollow fiber assays.

CONCLUSIONS:

Phytosomes are advanced form of herbal products that are better absorbed, utilized, and as a result produce better results than conventional herbal extracts. These are produced via a conventional process where potential herbal extracts are bound to phospholipids generally phosphatidylcholine which is also the principal constituent of human cell wall. The effectiveness of any herbal product (or medication) is dependent upon delivering an effective level of the active compounds. What the phytosome process produces is a little cell whereby the valuable components of the herbal extract are protected from destruction by digestive secretions and gut bacteria. They are cell membrane building blocks, making up the matrix into which fit a large variety of proteins that are enzymes, transport proteins, receptors, and other biological energy converters. In humans and other

higher animals the phospholipids are also employed as natural digestive aids and as carriers for both fat-miscible and water miscible nutrients. Increased bioavailability of the phytosomes over the simpler, noncomplex plant extracts has been demonstrated by pharmacokinetic (tissue distribution) and activity studies, conducted in animals as well as in humans. Phytosome has an added dimension; the proven health giving activity of the phospholipids themselves.

REFERENCES

1. R. Schandalik, G. Gatti, and E. Perucca. Pharmacokinetics of silybin in bile following administration of silipide and silymarin in cholecystectomy patients. Arzneim Forsch 1992.**42(7)**:964-8.
2. N. Barzaghi, et al. Pharmacokinetic studies on IdB 1016, a silybin-phosphatidylcholine complex, in healthy human subjects. Eur J Drug Metab Pharmacokinet 1990.**15(4)**:333-8.
3. S. Mascarella, et al. Therapeutic and antilipoperoxidant effects of silybin-phosphatidylcholine complex in chronic liver disease: Preliminary results. Curr Ther Res 1993.**53(1)**:98-102.
4. A. Vailati, et al. Randomized open study of the dose-effect relationship of a short course of IdB 1016 in patients with viral or alcoholic hepatitis. Fitoterapia 1993.**44(3)**:219-28.
5. C. Marena and P. Lampertico. Preliminary clinical development of Silipide: A new complex of silybin in toxic liver disorders. Planta Medical 1991.**57(S2)**:A124-5.
6. R.M. Facino, et al. Free radicals scavenging action and anti-enzyme activities of procyanidines from Vitis vinifera. A mechanism for their capillary protective action. Arzneim Forsch 1994.44:592-601.
7. C. Manach, A. Scalbert, C. Morand, et al. Polyphenols: food sources and bioavailability. Am J Clin Nutr 2004.79:727-747.
8. E. Bombardelli, S.B. Curri, Della R Loggia, et al. Complexes between phospholipids and vegetal derivatives of biological interest. Fitoterapia 1989.90:1-9.
9. P.M. Kidd. Phosphatidylcholine (Monograph). In: K. Czap, A.L. Miller, K.A. Head, et al, eds. Alternative Medicine Review Monographs Volume One. Dover, ID: Thorne Research, Inc. 2002:310-315.
10. P.M. Kidd. Glutathione (Monograph). In: K. Czap, A.L. Miller, K.A. Head, et al, eds. Alternative Medicine Review Monographs Volume One. Dover, ID: Thorne Research, Inc.. 2002:184-192.
11. H. Hikino, Y. Kiso, H. Wagner, M. Fiebig. Antihepatotoxic actions of flavonolignans from Silybum marianum fruits. Planta Med 1984.50:248-250.
12. 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 1989.55:420-422.
13. P.M. Kidd. Phosphatidylcholine: a superior protectant against liver disease. Altern Med Rev 1996. 1:258-274.
14. S. Malandrino, G. Pifferi. IdB-1016. Drugs Future 1990. 15:226-227.
15. B. Gabetta, G.F. Zini, G. Pifferi. Spectroscopic studies on IdB 1016, a new flavanolignan complex. Planta Med 1989.55:615.
16. Indena. Siliphos (TM). From Silybum marianum (L.) Gaertn. A new natural preventive targeted at the liver. Seattle, WA: Indena USA Inc.. 2004. www.indenausa.com
17. P. Morazzoni, A. Montalbetti, S. Malandrino, G. Pifferi. Comparative pharmacokinetics of silipide and silymarin in rats. Eur J Drug Metab Pharmacokinet 1993.18:289-297.
18. P. Morazzoni, M.J. Magistretti, C. Giachetti, G. Zanolo. Comparative bioavailability of Silipide, a new flavanolignan complex, in rats. Eur J Drug Metab Pharmacokinet 1992. 17:39-44.
19. N. Barzaghi, F. Crema, G. Gatti, et al. Pharmacokinetic studies on IdB 1016, a silybinphosphatidylcholine complex, in healthy human subjects. Eur J Drug Metab Pharmacokinet 1990.15:333-338.
20. D. Savio, P.C. Harrasser, G. Basso. Softgel capsule technology as an enhancer device for the absorption of natural principles in humans. A bioavailability cross-over randomised study on silybin. Arzneimittelforschung 1998.48:1104-1106.
21. P. Morazzoni, E.M. Martinelli. IdB 1108-comparative bioavailability with IdB 1316 in rats. Indena Report 1989. Seattle, WA: Indena USA Inc. www.indenausa.com
22. P. Morazzoni, A. Montalbetti, S. Malandrino, et al. Comparative biliary excretion of silybin after single oral doses of sililipide and silymarin in rats. First Intl. Symposium on Natural Drugs and the Digestive Tract, Naples, Italy. Seattle, WA: Indena USA Inc.. 1992. www.indenausa.com
23. R. Schandalik, G. Gatti, E. Perucca. Pharmacokinetics of silybin in bile following administration of silipide and silymarin in cholecystectomy patients. Arzneimittel for schung 1992.42:964-968.
24. R. Schandalik, E. Perucca. Pharmacokinetics of silybin following oral administration of silipide in

patients with extrahepatic biliary obstruction. Drugs Exp Clin Res 1994.20:37-42.

25. C. Marena, M. Lampertico. Preliminary clinical development of silipide: a new complex of silybin in toxic liver disorders. Planta Med 1991.57:A 124-A125.
26. R. Marcelli, P. Bizzoni, D. Conte, et al. 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 1992.1:131-135.
27. G. Buzzelli, S. Moscarella, A. Giusti, et al. A pilot study on the liver protective effect of silybinphosphatidylcholine complex (IdB 1016) in chronic active hepatitis. Int J Clin Pharmacol Ther Toxicol 1993.31:456-460.
28. S. Moscarella, A. Giusti, F. Marra, et al. Therapeutic and antilipoperoxidant effects of silybinphosphatidylcholine complex in chronic liver disease: preliminary results. Curr Ther Res 1993.53:98-102.
29. A. Vailati, L. Aristia, E. Sozze, et al. Randomized open study of the dose-effect relationship of a short course of IdB 1016 in patients with viral or alcoholic hepatitis. Fitoterapia 1993.94:219-228.
30. G. Buzzelli, S. Moscarella, S. Barbagli, et al. Therapeutic effect of silipide in patients with chronic hepatitis C non-responders (NRs) to interferon (IFN) treatment. J Hepatol 1994.21:17.
31. R. Orlando, A. Fragasso, M. Lampertico, et al. Pharmacokinetic studies of silybinphosphatidylcholine complex (IdB 1016) in liver cirrhosis after multiple doses. Med Sci Res 1991.19:827-828.
32. R. Orlando, A. Fragasso, M. Lampertico, et al. Silybin kinetics in patients with liver cirrhosis: a comparative study of a silybin-phosphatidylcholine complex and silymarin. Med Sci Res 1990. 18:861-863.
33. M. Conti, S. Malandrino, M.J. Magistretti. Protective activity of silipide on liver damage in rodents. Jpn J Pharmacol 1992.60:315-321.
34. F. Enjalbert, S. Rapior, J. Nouguier-Soule, et al. Treatment of amatoxin poisoning: 20-year retrospective analysis. J Toxicol Clin Toxicol 2002.40:715-757.
35. B. Schwitters and J. Masquelier. OPC in Practice: Biflavanols and Their Application. Alfa Omega, Rome, Italy, 1993.
36. C. Corbe, J.P. Boisin and A. Siou. Light vision and chorioretinal circulation. Study of the effect of procyanidolic oligomers (Endotelon). J Fr Ophtalmol 1988.11:453-60.
37. J.P. Boissin, C. Corbe and A. Siou: Chorioretinal circulation and dazzling: use of procyanidol oligomers. Bull Soc Ophtalmol Fr 1988.88:173-4,177-9.
38. T. Weihmayr and E. Ernst. Therapeutic effectiveness of Crataegus. Fortschr Med 1996.114:27-9.
39. U. Schmidt, et al. Efficacy of the Hawthorn (Crataegus) preparation LI 132 in 78 patients with chronic congestive heart failure defined as NYHA functional class II. Phytomed 1994.1(1):17-24.
40. M. Schussler, J. Holzl, U. Fricke: Myocardial effects of flavonoids from Crataegus species. Arzneim Forsch 1995.45:842-5.
41. M.G. Hertog, et al. Dietary antioxidant flavonoids and risk of coronary heart disease: the Zutphen Elderly Study. Lancet 1993.342:1007-11.
42. J. Wegrowski, A.M. Robert and M. Moczar. The effect of procyanidolic oligomers on the composition of normal and hypercholesterolemic rabbit aortas. Biochem Pharmacol
43. G. Scambia, R. De Vincenzo, F.O. Ranelletti, et al. Antiproliferative effect of silybin on gynaecological malignancies: synergism with cisplatin and doxorubicin. Eur J Cancer 1996.32A:877-882.
44. R.E. Singh R. Agarwal. Prostate cancer prevention by silibinin. Curr Cancer Drug Targets 2004.4:1-11.

