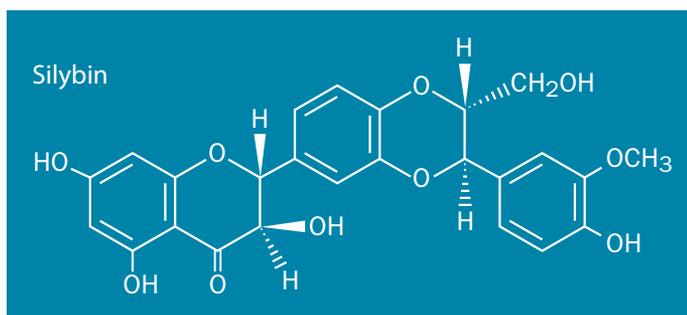


Silybin-Phosphatidylcholine Complex

Introduction

The fruit of the milk thistle plant (*Silybum marianum*, family Asteraceae/Compositae) has been a liver support remedy for 2,000 years.¹ The standardized extract known as silymarin contains three flavonoids of the flavonol subclass. Silybin predominates, followed by silydianin and silychristin. Silybin is

an effective antioxidant, conserving glutathione (GSH) in liver cells while stabilizing the liver cell membranes against oxidative attack.¹ Animal experiments have shown silybin blocks the oxidative toxicities of acetaminophen, alcohol, carbon tetrachloride, and the mushroom toxins phalloidin and alpha-amanitin.²⁻⁴ These findings correlate with decades of clinical observations that silybin improves survival after ingestion of deathcap mushrooms (*Amanita* species).⁵ Although silybin is the most potent of the flavonoids in milk thistle, like other flavonoids it is not well-absorbed. The utilization of non-phytosome silybin intravenously in mushroom-toxic patients (at 20-50 mg/kg/day) or of high-dose silymarin at 600 mg/day in diabetic patients has resulted in meaningful symptom improvement,⁶ presumably because the preparations were given either intravenously or at high oral doses. However, silybin-phosphatidylcholine complexed as a phytosome provides significant liver protection and enhanced bioavailability over conventional silymarin.



Biochemistry

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.⁷ 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, because flavonoid molecules typically have poor miscibility with oils and other lipids, they are severely limited in their ability to pass across the lipid-rich outer membranes of the enterocytes of the small intestine.

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.⁸ 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.

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.⁹ The intakes of phytosome preparations sufficient to provide reliable clinical benefit often also provide substantial PC intakes.¹⁰

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 phytochemicals, but without specifically bonding to them.¹⁰ See Kidd for a more complete review of phytosomes.¹⁰

Pharmacokinetics

The animal and human pharmacokinetics of the silybin phytosome complex have been reviewed in depth.¹¹ With respect to bioavailability, it is the most thoroughly researched of the existing phytosome preparations. For equal quantities of silybin taken by mouth, the phytosome form achieves markedly higher plasma levels of silybin than does the conventional, non-phytosome form.

The comparative uptakes of silybin from the phytosome form versus the non-phytosome form were investigated in two human studies. In the first, young healthy subjects (ages 16-26, n=8) took single 360-mg doses of silybin by mouth, either as the phytosome or as conventional silybin.¹² After eight hours the plasma silybin level achieved from the phytosome was almost three times that of the non-complexed silybin. By measuring the total area under the curve (AUC), it was determined that silybin is absorbed almost five times better from its phytosome than its conventional form.

The second human pharmacokinetic study was conducted with the same healthy young volunteers.¹² In this study, rather than a single dose of 360 mg, the silybin dose was 240 mg daily (120 mg every 12 hours) for eight days. This pattern of daily intake achieved high plasma concentrations and high total absorption on the

eighth day, matching those attained by the single higher dose (360 mg) given for one day, indicating no apparent decline in absorption efficiency after multiple days of intake.

Beyond improved delivery of silybin into the circulation, the silybin phytosome more capably delivers silybin to the liver. This was demonstrated by collecting bile secreted from the working livers of nine patients who had earlier undergone surgical gallbladder removal (necessitated by gallstones); thus, the patients were already equipped for bile collection.¹³ They were given single oral doses of 120 mg silybin, either as silybin phytosome or conventional silymarin. Bile collected over 48 hours contained 11 percent of the total dose of silybin from the phytosome form, compared to three percent from the non-complexed silybin source. In this study the plasma silybin level from the conventional silymarin dosing was almost undetectable, suggesting a 120-mg oral dose of silybin as silymarin may not be clinically effective.



Silybin collected in the bile is a valid measure of silybin that has traversed the liver tissue. Therefore, these data suggest the human liver receives about a four-fold higher exposure to silybin coming from phytosomes than from non-complexed silymarin.¹² The bile clearance data also are consistent with silybin's 4.6-times greater plasma bioavailability from intestinal absorption.¹²

In another study by the same group,¹⁴ 14 volunteers with cholestasis took only the silybin phytosome (120 mg silybin orally as a single dose) and showed rapid and substantial plasma absorption of silybin that peaked at 3-4 hours. Probably because the subjects were not secreting silybin into bile, relatively high levels persisted in the plasma up to 24 hours.

Mechanisms of Action

The liver is exceptionally vulnerable to toxic attack as hepatocytes continually sort, separate, metabolize, or store a variety of substances that reach the liver directly following absorption into the blood. Some,

such as triglycerides and fat-soluble vitamins, are packaged by the hepatocytes into lipoprotein particles and dispatched to other tissues. Others pose a toxic threat until they can be detoxified. The liver's position immediately "downstream" from the intestine puts it at risk from food-borne toxic agents. In addition to food-borne toxins, such as herbicide and pesticide residues, artificial preservatives, and other synthetic food additives, the liver must deal with other toxins that enter the body via diverse routes. These can include alcohol, cigarette-smoke toxins, street drugs, viral and bacterial antigens, heavy metals, solvent pollutants, and over-the-counter and prescription pharmaceuticals. During the detoxification process, glutathione, the key antioxidant in the liver's parenchymal cells, is directly or indirectly consumed.¹⁵

The antioxidant capacity of silymarin's flavonoids substantially boosts the liver's resistance to toxic insults.¹⁶ It is now known that silybin is the most potent of the three flavonoids in silymarin.⁴ Silybin has been extensively researched and found to have impressive bioactivity, albeit limited by poor bioavailability. In its native form within the milk thistle fruit, silybin occurs primarily complexed with sugars, as a flavonyl glycoside or flavonolignan. As a silybin-phosphatidylcholine complex, silybin protects the liver by conserving glutathione in the parenchymal cells, while PC helps repair and replace cell membranes.¹⁷ These constituents likely offer the synergistic benefit of sparing liver cells from destruction.

Clinical Indications

The silybin phytosome complex demonstrates better results for lowering liver enzymes, albeit in relatively small clinical trials.^{11,18-23} The phytosome form has produced degrees of symptomatic improvement in clinical trials of liver cirrhosis and alcoholic, iatrogenic, and viral hepatitis (types A, B, and C).¹⁸⁻²³ Taken altogether, the trial data suggest liver damage indicators in patients with acute or chronic hepatitis B and/or C will respond to 800-1,600 mg/day of silybin-phosphatidylcholine (providing 240-480 mg/day silybin) over 7-120 days.^{19,20,22,23}

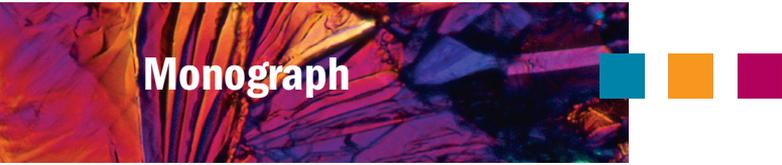
Hepatitis

Findings from human studies indicate oral silybin as Siliphos[®] has markedly greater benefit, milligram for milligram, than does non-complexed silybin from silymarin.

In 1991, Marena and Lampertico reported on several studies involving a total of 232 patients with liver disorders treated with phytosomal silybin.¹⁸ Daily intakes ranged from 240-360 mg silybin in phytosome form, taken for up to 150 days between meals. Control subjects were also treated with either non-complexed silybin (n=49) or with placebo or no treatment (n=117). Evaluation of efficacy was based primarily on serum liver enzyme levels, namely aspartate aminotransferase (AST), alanine aminotransferase (ALT), and gamma-glutamyltranspeptidase (GGT). The investigators came to the conclusion that phytosomal silybin had "significant clinical effect."¹⁷ In the population of patients with alcoholic hepatitis, serum AST and ALT returned to normal significantly faster with Siliphos than the reference preparation of non-phytosomal silybin. In another study, patients with acute viral hepatitis (A or B types) fared better on the phytosomal preparation compared to placebo-treated subjects. Similar findings emerged for patients with hepatitis of undetermined cause (so-called iatrogenic cases).

In 1992, researchers at universities in Milan and Bari reported on a controlled study of chronic persistent hepatitis.¹⁹ Patients were randomized to receive either 240 mg silybin phytosome (n=31) or placebo (n=34), one capsule 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 the placebo group, and no patient discontinued the trial due to adverse effects.

A short-term, 1993 pilot study, representing a collaboration between Indena[®] (a manufacturer of a wide range of botanical extracts, including Siliphos) and researchers at the University of Florence, examined the effect of silybin phytosome on 20 patients with chronic active hepatitis (B and/or C).²⁰ During this one-week trial, 10 patients received 480 mg silybin phytosome daily and 10 received placebo. A reduction in serum levels of ALT (29%), AST (25%), and GGT (20%) was observed in the silybin group. Plasma levels of silybin



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were markedly increased at day 7, attaining levels consistent with those measured in the pharmacokinetic studies.¹² In the placebo group, only GGT showed a significant decrease (8% compared to 20% in the silybin group).²⁰ This study also measured serum malondialdehyde (MDA) levels, a byproduct of lipid peroxidation. Although serum MDA fell in the silybin group, it was not statistically significant.

In another very small pilot study, eight patients with chronic active hepatitis (B and/or C) were treated with phytosomal silybin at a daily dose of 240 mg silybin for two months.²¹ Liver enzymes ALT and AST were significantly reduced, while reductions in GGT and MDA did not attain statistical significance. As with the patients in the previous study, baseline MDA levels were very high when the study began. The findings from these two small pilot studies suggest phytosomal silybin is a valuable component of an integrated approach to managing active infection with hepatitis B and/or C viruses. These findings deserve replication in larger and longer studies.

Data particularly useful in establishing dosing recommendations came from a larger 1993 hepatitis trial at the University of Pavia involving 54 patients.²² Patients with chronic hepatitis of either viral or alcoholic origin were randomly assigned to one of three groups. One group (n=19) received phytosomal silybin at 160 mg daily; another group (n=17) received 240 daily; and the third group (n=18) received 360 mg daily. The trial lasted two weeks, with enzyme indicator testing done after weeks 1 and 2. Despite the short duration of the trial, AST was significantly lowered by all dosages. At the two higher doses of 240 and 360 mg daily (but not at 160 mg daily) ALT and GGT were also significantly lowered. Furthermore, at the two higher doses after one week a dose-effect relationship was seen for AST and GGT (although not for ALT) – the higher the dose, the greater the decrease in liver enzymes. In this trial, four of 60 patients experienced adverse effects and two dropped out of the 360-mg group before the end of the first week. The researchers concluded that using phytosomal silybin, an intake of 160 mg silybin daily (one 80-mg capsule twice daily, taken between meals) provided a good maintenance intake. They suggest for better and more reliable results the 240-mg daily intake might be appropriate, and for more difficult cases the 360-mg intake of phytosomal silybin might be indicated.

A small, double-blind trial, published only in abstract form, suggests phytosomal silybin might be useful against hepatitis C in chronically infected patients who do not benefit from interferon treatment.²³ Ten patients who failed to measurably respond to recombinant interferon alpha 2b were studied according to a crossover, randomized, double-blind trial design. After 6-12 months of interferon withdrawal, patients were randomly assigned to receive either phytosomal silybin (360 mg silybin daily) or placebo for two months. After a one-month washout period subjects were crossed over to the other treatment. After statistical analysis phytosomal silybin significantly lowered both ALT and AST, while the placebo failed to do so.

Cirrhosis

Phytosomal silybin is likely safe for cirrhotic patients. Researchers at the University of Padua collaborated with Indena to study uptake of silybin phytosome in 10 patients with compensated liver cirrhosis (Child's Grade A).²⁴ The patients first received a single 120-mg dose of silybin as phytosome daily, and blood silybin levels were monitored. This was followed by a multiple-dose study in which patients received a 120-mg dose twice daily for eight days. The patients absorbed the silybin phytosome as well as healthy subjects, although there was great variability from patient to patient.

In this study, the profile of data from the eight-day dosing period did not show significant differences from the first day's data.²⁴ From this finding the researchers concluded that (on average) patients were not accumulating silybin in poorly functioning livers, nor were any clinically adverse effects reported. Another study on cirrhotic patients (n=9) used a higher dose of silybin as phytosome (360 mg) for one day.²⁵ Great inter-patient variability was found, with no clinically adverse effects. Since hepatitis patients can develop adverse effects at this high intake,²² such short-term experience does not prove this dosage is safe for long-term use by patients with cirrhosis.

Side Effects and Toxicity

This phytosomal form of silybin has been studied for safety.^{4,18,26} Overall, it is well tolerated in humans. According to researchers Marena and Lampertico,¹⁸ 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 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 percent of patients who received non-complexed silybin and 5.1 percent of patients on placebo. In other words, adverse effects of phytosomal silybin were essentially the same as placebo. The phytosomal silybin produced no clinically relevant blood changes in these patients.

Phytosomal silybin has also proven safe in traditional toxicological tests. Oral acute toxicity is >5,000 mg/kg body weight in rats, dogs, and monkeys. After 13-week subacute toxicity studies the preparation was found safe for rats and monkeys at oral doses up to 2,000 mg/kg body weight/day. In 26-week chronic toxicity studies, oral doses up to 1,000 mg/kg body weight/day were well tolerated in rats and dogs. In another 26-week oral toxicity study, rats were fed a daily 2,000 mg/kg body weight dose of Siliphos, equivalent to 160 g daily for a 176-pound (80 kg) human. As published by Indena, body weight, liver weight, and enzyme indicators of liver damage (AST, ALT) remained within the normal, healthy range of the untreated control rats.²⁷ Pharmacological studies in mice, rats, and dogs indicate phytosomal silybin does not adversely affect central nervous system, cardiovascular, or respiratory functions, and does not influence stomach emptying or intestinal motility, at oral doses as high as 1,000 mg/kg body weight. The silybin-PC complex had no evident adverse effects on reproduction in rats and showed no mutagenic effects in several test systems.²⁶

Silymarin and silybin are well tolerated. Silybin intakes up to 1,080 mg/day as phytosome are well tolerated even by patients with compensated cirrhosis.²⁸ A 2007 trial that utilized the silybin phytosome for prostate cancer determined that up to 13,000 mg/day of the phytosome (providing about 3,900 mg/day of silybin) is well tolerated by patients with advanced cancer.²⁹

Dosage

While silymarin (typical standardized milk thistle extract) must be taken at doses of approximately 420 mg daily to achieve benefit, silybin (complexed with phosphatidylcholine) can produce benefit at intakes as

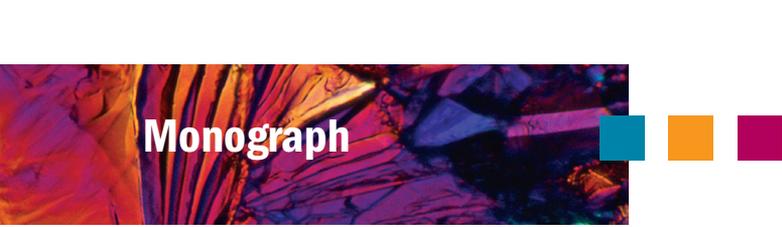
low as 120 mg (400 mg silybin-PC complex) daily, and can be safely administered regularly at doses of 240-360 mg (800-1,200 mg silybin-PC complex) daily.

Acknowledgement

For more extensive reviews of silybin-phosphatidylcholine complex and phytosome complexes in general, see Kidd’s reviews in *Altern Med Rev*, volumes 10(3) and 14(3), excerpts of which appear in this monograph.

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