

A Review of the Bioavailability and Clinical Efficacy of Milk Thistle Phytosome: A Silybin-Phosphatidylcholine Complex (Siliphos®)

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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 fruit of the milk thistle plant (*Silybum marianum*, Family Asteraceae) contains flavonoids that are proven liver protectants. The standardized extract known as silymarin contains three flavonoids of the flavonol subclass. Silybin predominates, followed by silydianin and silychristin. Although silybin is the most potent of the flavonoids in milk thistle, similar to other flavonoids it is not well-absorbed. Silybin-phosphatidylcholine complexed as a phytosome provides significant liver protection and enhanced bioavailability over conventional silymarin. (*Altern Med Rev* 2005;10(3):193-203)

Introduction

Most of the bioactive constituents of phyto-medicines are flavonoids (e.g., anthocyanidins from bilberry, catechins from green tea, silymarin from milk thistle). However, many flavonoids are poorly absorbed.¹ 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.

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.² 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.

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

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Thorne Research is among the supplement manufacturers that supply Siliphos

alcoholic hepatic steatosis, drug-induced liver damage, and hepatitis.³ The intakes of phytosome preparations sufficient to provide reliable clinical benefit often also provide substantial PC intakes.

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.

The Mechanism of Hepatic Detoxification

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.⁴

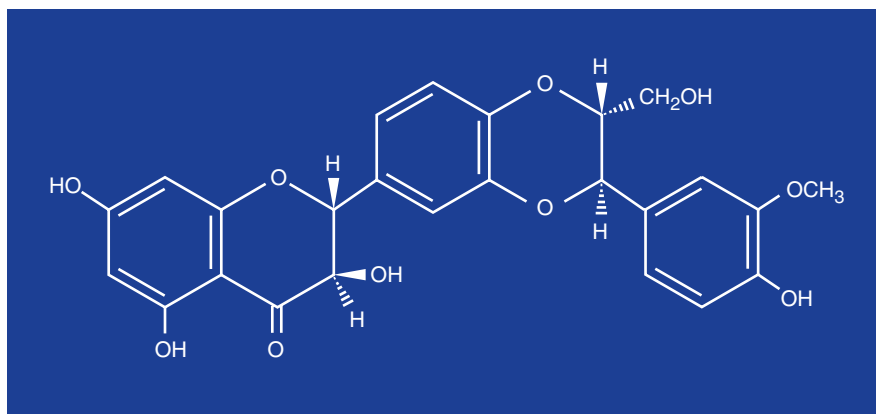
The liver's vulnerability to toxic agents is often compounded by its efforts to detoxify them. Its sophisticated cytochrome P450 enzyme system evolved to detoxify and excrete excess amounts of hormones and other substances that are naturally produced in the body, as well as synthetic chemicals. However, in attempting to neutralize certain toxins, P450 enzymes can chemically transform such substances, making them more toxic. The consequence can be uncontrolled depletion of glutathione and other antioxidants, resulting in hepatocyte destruction.

Figure 1. *Silybum marianum*



Silybum marianum Contains Premier Liver-Protectant Flavonoids

The fruit of the milk thistle plant (*Silybum marianum*, Family Asteraceae) (Figure 1) contains flavonoids known for hepatoprotective effects.⁵ The antioxidant capacity of silymarin substantially boosts the liver's resistance to toxic insults.⁶ Silymarin primarily contains three flavonoids of the flavonol subclass (having a fully saturated C-ring). Silybin predominates (Figure 2), 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.⁵ Silybin protects the liver by conserving glutathione in the parenchymal cells, while PC helps repair and replace cell membranes.⁷ These constituents likely offer the synergistic benefit of sparing liver cells from destruction. In its native form within the milk thistle fruit,

Figure 2. Structure of Silybin

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.

Pharmacokinetics of Silybin-Phosphatidylcholine Complex

In 1990, Malandrino et al succeeded in improving the bioavailability of silymarin extract by complexing it with soy PC – a phytosome.⁸ 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.⁹ This property predicts the enhanced ability of phytosomes to cross cell membranes and enter cells.

Animal Studies

The superior bioavailability of silybin complexed with PC over non-complexed silybin has been documented through pharmacokinetic studies conducted in rats and humans. Figure 3 illustrates that, in rats, a large dose of silybin given orally as plain silymarin remained virtually undetectable in the plasma for the six-hour experiment.^{10,11} In marked contrast, when the same amount of silybin (200 mg per kg body weight) was given as Siliphos®, a silybin-PC phytosome, 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.

The superior absorption of the silybin from Siliphos is reflected in its clearance in the urine. Figure 4 illustrates 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.¹²

Siliphos has been demonstrated to reach the liver, its target organ. Silybin was substantially present in bile fluid two hours following the administration of Siliphos and the liver continued to secrete silybin into the bile during the entire study.¹¹ Silybin, given as the non-complexed silymarin, was barely detectable in the bile during the same period.

From these single-dose, bioavailability studies several key points are evident. Silybin, when taken

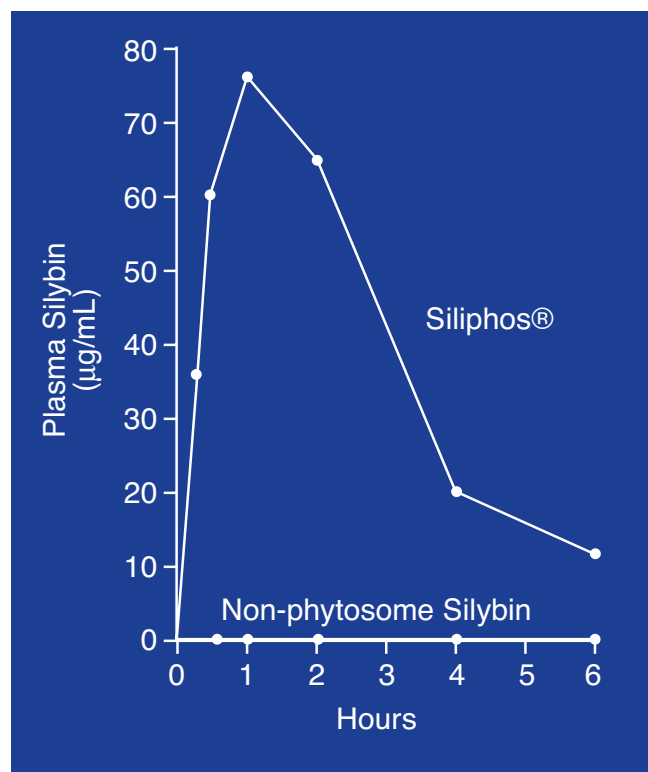
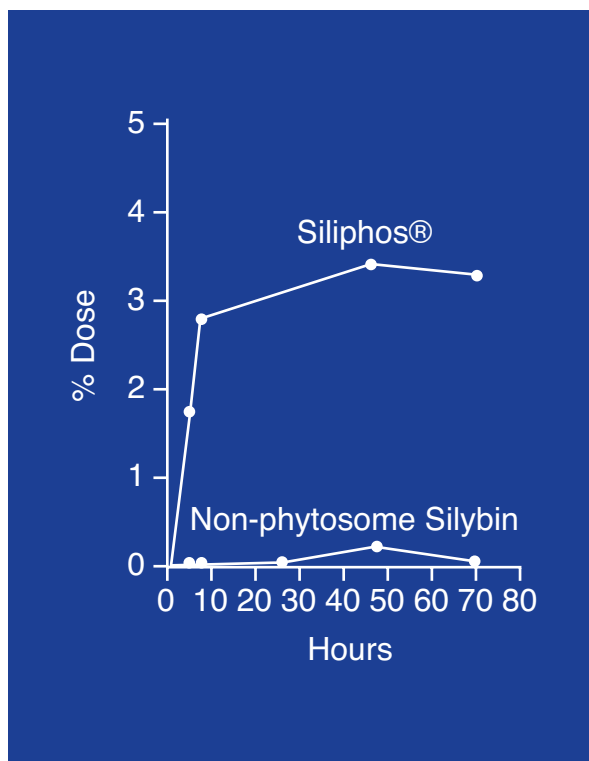
Figure 3. Relative Plasma Levels of Total Silybin in Rats after Dosing with Siliphos® or Non-complexed Silybin10

Figure 4. Relative Percentages of Silybin Recovered in the Urine after Dosing with Phytosomal Silybin or with Silybin from Silymarin in Rats¹⁰



by mouth, is poorly absorbed even at a very high intake (200 mg/kg body weight of the rat, equivalent to a 16-gram dose for a 176-pound human). However, when taken by mouth as phytosomes bound to PC, silybin is well absorbed and detected in the blood within the first hour.

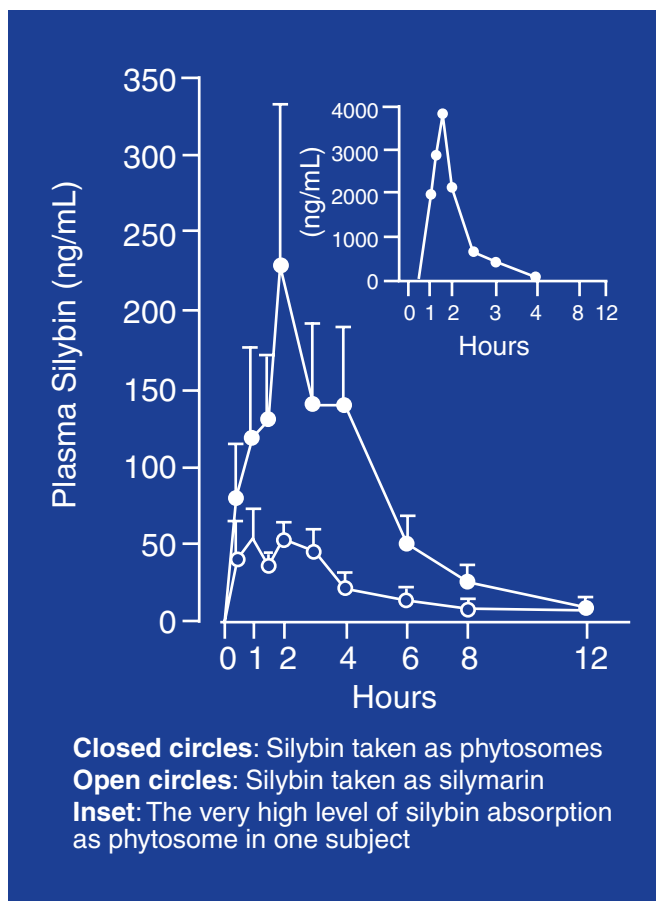
These rat studies yielded another important finding – that phytosomal silybin rapidly reaches the liver, traverses the liver cells, and appears in the bile within two hours. The amount of silybin reaching the bile from phytosome dosing is at least 6.5 times greater than that from non-complexed silybin (13% versus 2%, over 24 hours).¹¹ Some portion of the phytosomal silybin remains in the liver for at least 24 hours.

Silybin entering the body as phytosomes also clears the body via the kidneys. It appears in the urine within a few hours and continues to clear via the urine for up to three days.¹⁰

Human Studies

Silybin in phytosome form is also well absorbed in humans.^{13,14} Pharmacokinetic studies conducted with human subjects showed a pattern similar to rats. In the early studies (1990), eight healthy volunteers ages 16-26 took single 360-mg oral doses of silybin, either as phytosomes or non-complexed silymarin.¹³ The silybin from silymarin rose slightly in the plasma beginning one hour after dosing, and declined to minimal levels by eight hours (Figure 5, open circles). Silybin phytosome was substantially present in the plasma by one hour, peaked around two hours, and at eight hours was almost three times the level of silybin from silymarin (Figure 5, closed circles). By measuring the total area under the curve (AUC) for

Figure 5. Plasma Silybin Uptake in Healthy Humans



each line, it was determined that phytosomal silybin was absorbed 4.6 times better than the non-phytosome silybin from silymarin.¹³ This compares with an estimated 6.0-6.3 times better bioavailability in rats, as calculated from plasma uptake patterns¹⁵ and bile secretion.¹⁶ There was substantial variability among subjects, as reflected by the broad error bars in Figure 5; one subject had extremely high absorption (see the inset, Figure 5).

A further, multiple-dose study was conducted with these same healthy young volunteers.¹³ In place of a single dose of 360 mg, phytosomal silybin was given twice daily (120 mg every 12 hours, totaling 240 mg silybin daily) for eight days. This dosing pattern maintained the same high plasma concentrations and high total absorption attained by the single higher dose (360 mg) given for one day. There was no decline in absorption efficiency after multiple days of intake.

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.^{17,18} They were already “rigged” for such a study, with bile drained via a tube. 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 percent of the total dose. In the case of silymarin, approximately three percent of the silybin was recovered. These data suggest a four-times greater passage through the liver for phytosomal silybin. Also, the human bile data¹⁷ compare favorably with the human AUC data, which suggest a 4.6-times greater bioavailability from the phytosome form than the simple extract.¹³

A 1998 study suggests Siliphos may be more bioavailable when taken as a liquid in softgel form.¹⁴ Twelve healthy subjects were given a single dose of 80 mg silybin as phytosomes, either in softgel or two-piece hardgel capsules, then had blood samples taken for eight hours. Subsequently, they were crossed-over to the opposite product and sampled again. The maximum plasma concentration attained from the softgel

was three times greater than from the hardgel. Average AUC after the first hour for the softgel was more than twice that for the hardgel cap, suggesting faster absorption as well.

Clinical Efficacy of Silybin Phytosome

Findings from several studies with human subjects indicate that silybin taken by mouth 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.¹⁹ 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.”¹⁹ In the population of patients with alcoholic hepatitis, serum AST and ALT returned to normal significantly faster with Siliphos than with 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 the patients with hepatitis of undetermined cause (so-called iatrogenic cases).

In 1992, researchers at the Universities of Milan and Bari reported on a controlled study of chronic persistent hepatitis.²⁰ 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.

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).²¹ During this one-week trial, 10 patients received 480 mg silybin 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 were markedly increased at day 7, attaining levels consistent with those measured in the pharmacokinetic studies.¹³ In the placebo group only GGT showed a significant decrease (8% compared to 20% in the silybin group).²¹ 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 240 mg silybin for two months.²² 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 that 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.²³ 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 mg 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.

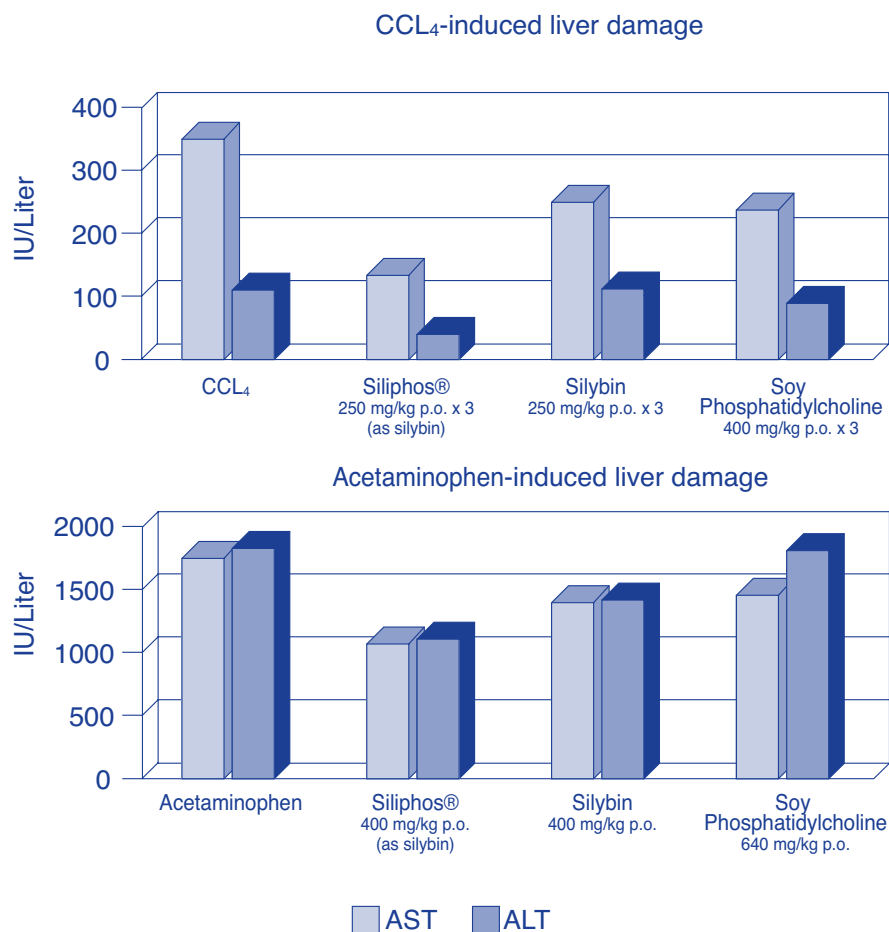
Furthermore, at the two higher doses a dose-effect relationship was seen for AST and GGT (although not for ALT) – the higher the dose, the greater the decrease in liver enzymes. These differences were evident after one week. In this trial, four of 60 patients experienced adverse effects and two dropped 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 suggested that for better and more reliable results the 240-mg daily intake might be appropriate. For more difficult cases the 360-mg intake of phytosomal silybin might be indicated, although there is greater possibility of adverse effects.

A small, double-blind trial, published only in abstract form, suggested phytosomal silybin might be useful against hepatitis C in chronically infected patients who did not benefit from interferon treatment.²⁴ Ten patients who had failed to measurably respond to recombinant interferon alpha 2b (3 million units three times weekly for six months) 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, the phytosomal silybin was found to significantly lower both ALT and AST, while the placebo failed to do so.

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).²⁵ The patients first received a single daily dose of 120 mg silybin phytosome, 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 were found to absorb 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.²⁵ From this finding the researchers concluded that (on average) patients

Figure 6. Silybin as Siliphos® Partially Protects against Experimental Liver Damage from Carbon Tetrachloride (top panel) or Acetaminophen (bottom panel)



Liver damage was monitored as blood levels of the standard indicator enzymes AST and ALT.¹⁰

were not accumulating silybin in poorly functioning livers, nor were any clinically adverse effects reported. Such short-term experience does not prove the supplement is safe for long-term use by a liver-compromised population. Another study by this group on cirrhotic patients (n=9) used a higher dose of silybin as phytosome (360 mg) for one day.²⁶ Great inter-patient variability was found, with no clinically adverse effects. Since hepatitis patients can develop adverse effects at this high intake,²³ such short-term experience does not prove the supplement is safe for long-term use by patients with cirrhosis.

Animal Studies on Siliphos

Silybin-phytosome complex has been shown to offer liver protection in laboratory rats. Rats fed the toxic solvent carbon tetrachloride or the potentially liver-toxic acetaminophen developed abnormally elevated levels of AST and ALT. When high-dose silybin (as Siliphos) was administered along with the toxic insult, the liver enzymes were significantly reduced (Figure 6).²⁷

Protective effects of phytosomal silybin were observed using rats pre-exposed to toxins such as praseodymium, galactosamine, and the mushroom poisons phalloidin and alpha-amanitin.⁵ This correlates with decades of clinical observations that silybin improves survival of humans exposed to deathcap mushroom (*Amanita* sp.) and other toxic mushrooms.²⁸

Correlating with the human trial findings that silybin protects the liver against alcohol toxicity,^{29,30} Siliphos blocked some adverse effects of ethanol in animal studies. For example, ethanol fed to rats in high doses raises liver

triglyceride (TG) levels. High TG levels are a proven risk factor for cardiovascular disease in humans. One study showed high-dose Siliphos fed to rats along with ethanol significantly blocked ethanol's TG-elevating effect (Figure 7).^{10,27}

In vitro Studies

Silybin's potent antioxidant activity is thought to account for much of its liver protection. One accepted experimental system for generating free radicals and calibrating antioxidants is the NADPH/iron effect on membranes prepared from rat liver cells. In this system, iron pulls electrons from the electron-rich NADPH molecule and the resultant molecules are used to peroxidize cell membranes. The main end-product of the membrane breakdown is MDA. Silybin added to this "test tube" system can block the formation of MDA (Figure 8).¹⁰

The silybin effect in blocking MDA is dose-dependent, with increasing concentrations of silybin having progressively greater blocking effect. Such dose-dependency makes the effect more relevant to the intact body. In liver parenchymal cells isolated from rats, silybin used in phytosome form entered the cells and protected against MDA formation from a variety of peroxidative toxins, including ADP/iron, cumene hydroperoxide, allyl alcohol, and bromotrichloromethane.³¹ Similar protection against peroxidation was observed in rats pretreated with the silybin-PC complex prior to the cells being isolated. Other research confirms silybin can actually trap free radicals within the membranes of liver cells, as such reactive molecular fragments are being generated from carbon tetrachloride and methylhydrazine.^{32,33}

Figure 7. Phytosomal Silybin Partially Protects against Alcohol-induced Increase of Liver Triglycerides^{10,27}

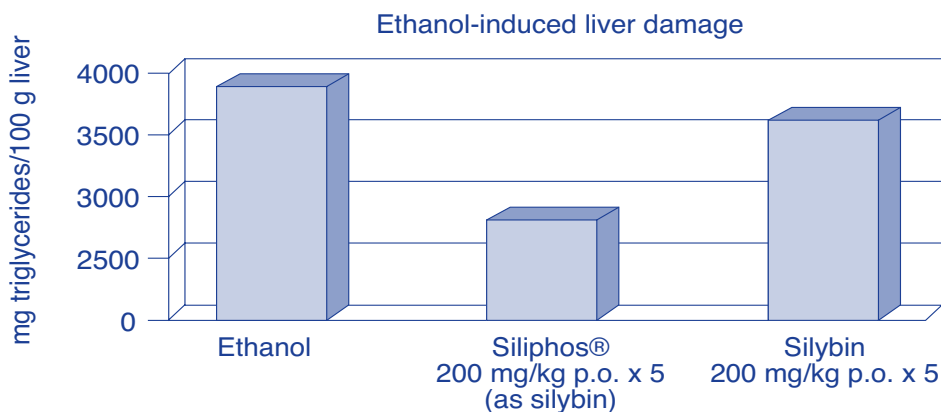
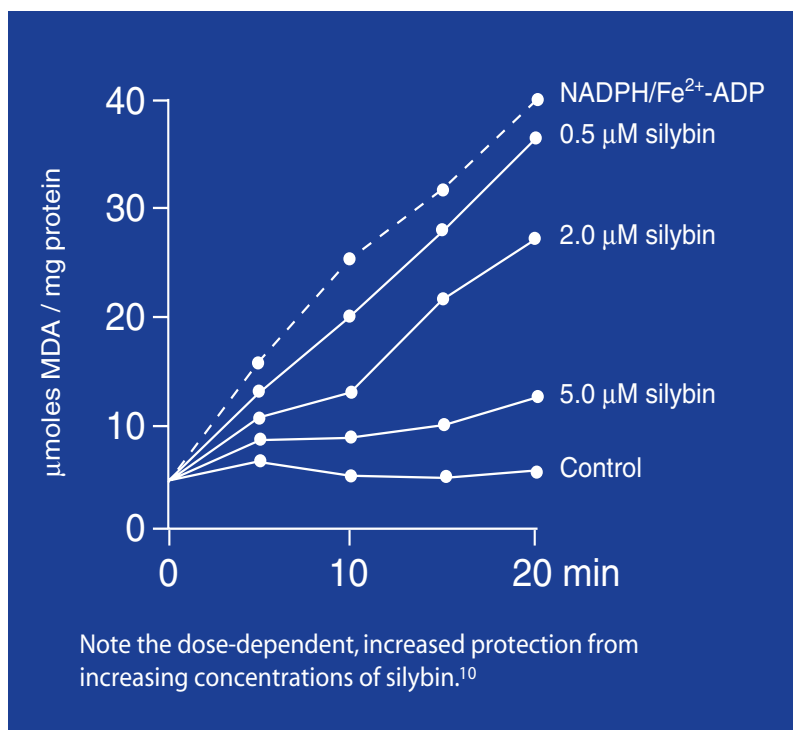


Figure 8. In vitro, Silybin Protects Rat Hepatocyte Membranes from Free Radical Peroxidative Attack



Safety and Tolerability of Silybin-PC Complex

This phytosomal form of silybin has been studied for safety.^{5,19,34} Overall, it is well tolerated in humans. According to researchers Marena and Lampertico,¹⁹ 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 percent of patients who received non-complexed silybin and 5.1 percent of patients on 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 per kg 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 per kg per day. In 26-week chronic toxicity studies, oral doses up to 1,000 mg per kg per day were well tolerated in rats and dogs. In another 26-week oral toxicity study, rats were fed a daily 2,000 mg per kg 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.¹⁰ 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 per kg. The silybin-PC complex had no evident adverse effects on reproduction in rats, and showed no mutagenic effects in several test systems.¹⁰

Conclusion and Future Research Direction

Silybin-PC complexed as a phytosome provides significant liver protection and enhanced bioavailability over conventional silymarin when taken orally. Phytosomal silybin is more rapidly absorbed than silymarin, perhaps more so when taken in soft-gels. It is also absorbed at least four times more completely than silymarin, reaching the liver rapidly and appearing in the bile within a few hours. While silymarin must be taken at doses of approximately 420 mg daily to achieve benefit, phytosomal silybin (Siliphos) can produce benefit at intakes as low as 120 mg daily, but can be safely administered at doses of 240-360 mg daily. Since adverse effects are possible at the higher intakes, monitoring would seem prudent for subjects having ongoing intakes above 240 mg daily.

In addition to direct hepatoprotective effects, silybin has iron-chelating capacity that could be investigated for management of chronic iron overload.³⁵ It is also under active investigation for cancer prevention and management,³⁶⁻³⁸ and has entered a Phase I clinical trial for treatment of prostate cancer.³⁹

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