

SILIPHOS®

FROM *SILYBUM MARIANUM* (L.) GAERTN.
A NEW NATURAL PREVENTIVE TARGETED AT THE LIVER



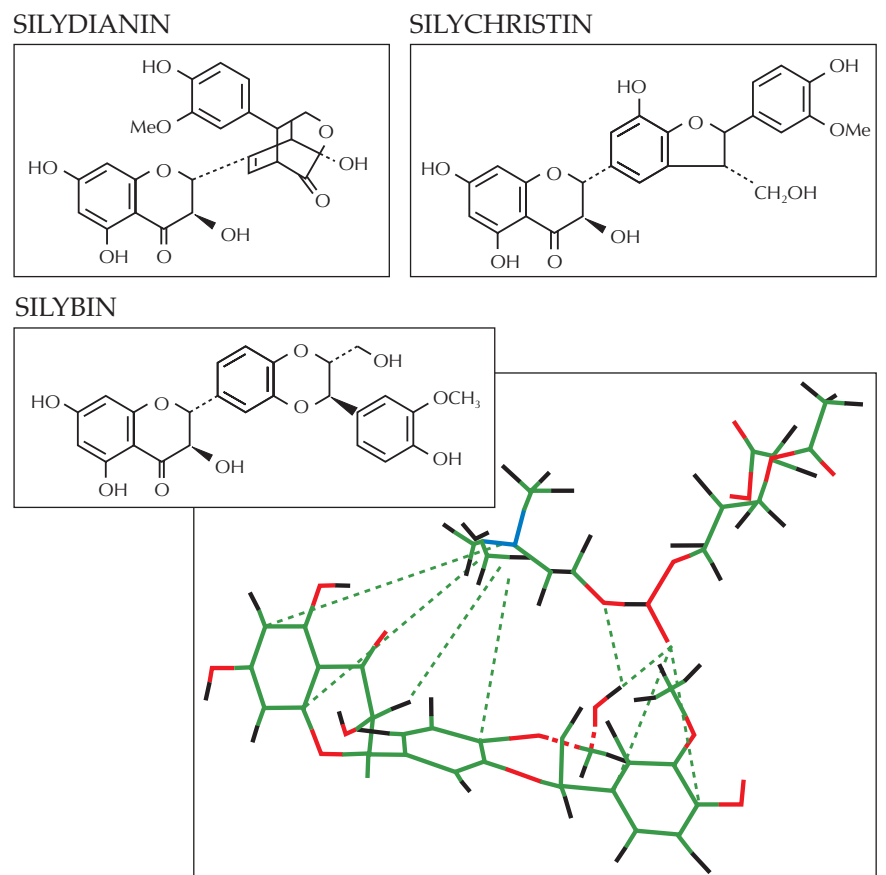


The liver, due to the vital role it plays in metabolism, is particularly exposed to the harmful action of endogenous and exogenous toxic substances. In fact, many potentially harmful molecules (alcohol, drugs, hormones, etc.) are metabolized by the liver and transformed into more hydro-soluble derivatives for subsequent biliary extraction and removal from the body. This detoxication process is achieved by a variety of enzymes (oxidizing, reducing, hydrolyzing or conjugating) located in the hepatic microsomes, part of the smooth endoplasmic reticulum of the liver cell. For this reason the upkeep of the integrity of the liver cell is necessary for the safeguarding of health. Several biochemical reactions involve as starters or intermediates various free radical species which constitute a continuous risk factor for the integrity of the hepatocytes.¹ Therefore, any prevention aimed at reducing potential damage to the liver and any substances contributing to its integrity are certainly of interest. Derivatives of the traditionally used European plant *Silybum marianum* (L.) Gaertn. (Asteraceae) occupy an eminent position in liver protection. The name *Silybum* derives from "sillybon" (tuft, pendant), an ancient Greek word used by Dioscorides (1 century A.D.) to indicate a thistle with white spotted leaves.

An old legend tells that these white marks and stripes on the leaves represent the drops of Mary's milk fallen from her breast while she was breastfeeding Jesus during their escape to Egypt.² Since ancient times *S. marianum* has been known and used to be recommended as an emetic. During the Middle Ages the plant was probably cultivated in monasteries and used for medicinal purposes: the roots, herb and leaves were recommended for swelling and erysipelas (St. Hildegard from Bingen, 1098-1179) or for the treatment of liver complaints (Lonicerus, John Gerard, Pietro Andrea Mattioli, XVI-XVII centuries). From 1755 onwards, the specific use of *S. marianum* fruit for the treatment of liver disease, disorders of the bile duct and spleen was documented.^{3,4} At present, the standardized extract (silymarin) obtained from the fruit of *S. marianum* and containing as main constituents silybin, silydianin

and silychristin (Fig. 1), is widely used in European medicine in the treatment of liver disease. The main constituent silybin has been subjected to several biochemical and pharmacological studies which have demonstrated its interesting properties but also its poor bioavailability. Complexation with soy phosphatidylcholine gives rise to the lipophilic complex⁵ (US Patent 4, 764, 508) which substantially improves the bioavailability of silybin. This results in a marked preventive action as observed in several models of liver intoxication including those with a strong involvement of oxidative stress.² In this way, the silybin-phosphatidylcholine complex SILIPHOS[®], containing 33% of silybin, endowed with antioxidant activity and, simultaneously, able to prevent cellular derangement by stabilizing the cell membranes and restoring the normal ultrastructure of the hepatocytes, plays a key role in the prevention of liver damage.

Fig. 1 From *Silybum marianum* to SILIPHOS[®].



TOXICOLOGY

SILIPHOS® was shown to be well tolerated in acute and long-term toxicity tests in rodents (Table 1) and in primates up to oral doses of 2000 mg/kg (as silybin).

The excellent tolerability of this complex was confirmed in volunteers at dosage up to 360 mg p.o. (as silybin) t.i.d. for three weeks.⁶

PHARMACOKINETICS

As demonstrated by pharmacokinetic studies in comparison with free silybin and silymarin, SILIPHOS® represents the most absorbable form of silybin known until now. In rats, after oral administration of 200 mg/kg of silybin, the plasma levels of this drug and its conjugated metabolites were below the analytical detection limit, while, after oral administration of SILIPHOS® (200 mg/kg as silybin) the plasma levels of silybin (free and total) were easily measurable (Fig. 2).

Furthermore, after oral administration of SILIPHOS®, the biliary elimination of silybin was not complete at 24 h

and accounted for about 3.7% of the administered dose (Fig. 3).

The compound was rapidly excreted in urine where at 72 h the amount recovered accounted for about 3.3% (Fig. 4). After administration of uncomplexed silybin, biliary and urinary elimination accounted for only 0.001% and 0.032%, respectively.⁷

The improvement of the oral bioavailability for SILIPHOS® is mainly dependent on a marked increase of its absorption in the gastrointestinal tract, most likely due to the lipophilic character of the complex. Also in comparison with silymarin, SILIPHOS® demonstrated a superior bioavailability which, as calculated for cumulative biliary excretion, resulted to be about 10-fold higher than that of the extract.⁸ SILIPHOS® shows the same pharmacokinetic profile in man. After oral treatment, the bioavailability in healthy volunteers, in cholecystectomised patients or in patients suffering from hepatic cirrhosis is comparable to that demonstrated in animal models.^{2,9,10}

After oral intake of SILIPHOS®, silybin appears rapidly in the bloodstream and is eliminated from the plasma with

a relatively short half-life. Silybin is metabolized extensively, most of the drug recovered by the systemic circulation being present as sulphate and/or glucuronide conjugates. Only a small fraction of the dosage could be recovered in urine indicating that silybin is mostly eliminated by biliary excretion.

Table 1 Twenty-six week oral toxicity study in rats.

Daily dose: SILIPHOS® 2000 mg/kg (as silybin)

	Males	Females
Body weight (g)		
Control	685.5 ± 78.0	306.6 ± 28.8
SILIPHOS®	636.5 ± 44.9	319.0 ± 25.4
Liver weight (g)		
Control	25.9 ± 3.7	12.1 ± 1.7
SILIPHOS®	23.2 ± 2.6	11.5 ± 1.3
Serum enzymes		
ALAT (U/L)		
Control	20.5 ± 2.9	23.7 ± 13.3
SILIPHOS®	21.9 ± 3.1	26.1 ± 7.5
ASAT (U/L)		
Control	33.6 ± 5.0	44.0 ± 23.8
SILIPHOS®	32.4 ± 5.9	34.9 ± 5.0

Fig. 2 Mean plasma levels of total silybin after treatment with SILIPHOS® and silybin in rats (n=6).

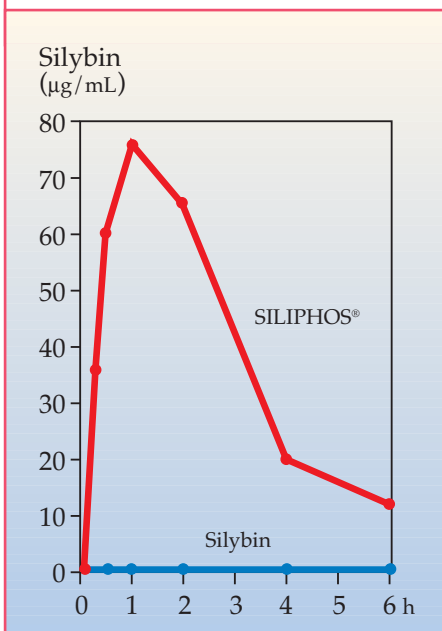


Fig. 3 Biliary excretion of total silybin after treatment with SILIPHOS® and silybin in rats.

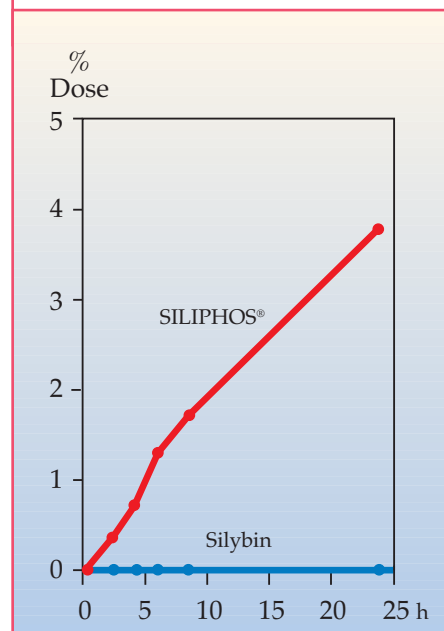
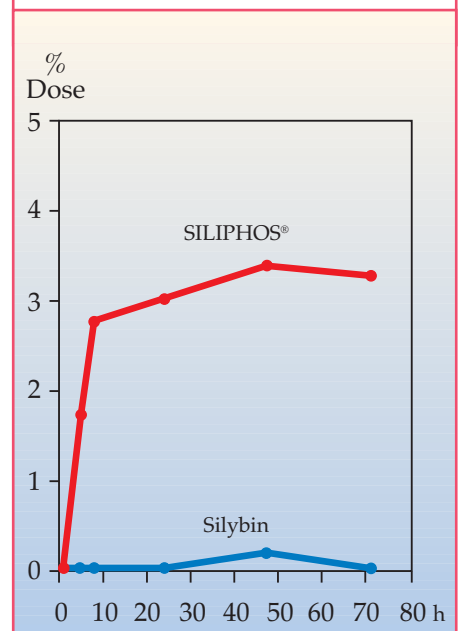


Fig. 4 Urinary excretion of total silybin after treatment with SILIPHOS® and silybin in rats.



PHARMACOLOGY AND MECHANISM OF ACTION

SILIPHOS® is to be considered a natural vehicle of silybin, the active botanical ingredient. SILIPHOS® allows silybin to reach the target organ, the liver, in concentrations which are reported to be effective in several models of liver intoxication^{11,12} (Fig. 5) and to fit with the most important molecular mechanisms observed *in vitro*, such as the antioxidant¹³⁻¹⁶ (Fig. 6, 7) and the stimulation of protein synthesis in hepatocytes¹⁷ (Fig. 8).

Fig. 5 Activity of SILIPHOS® on different experimental models of liver damage in rats.

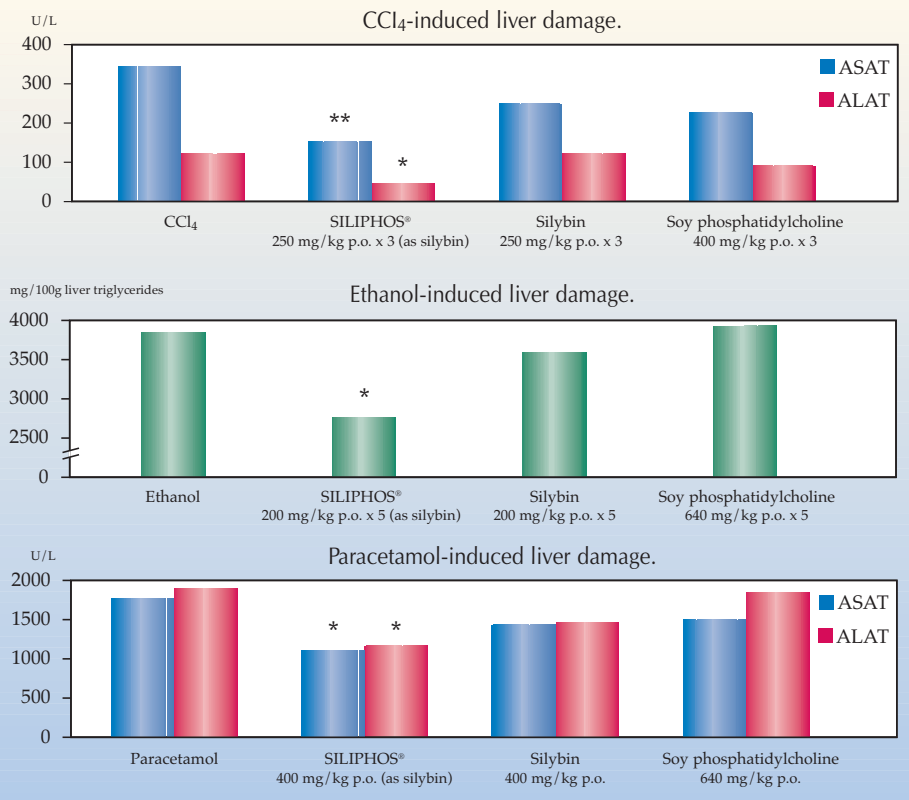


Fig. 6 *In vitro* effects of silybin on the malondialdehyde (MDA) formation induced by NADPH/Fe²⁺-ADP on rat liver microsomes.

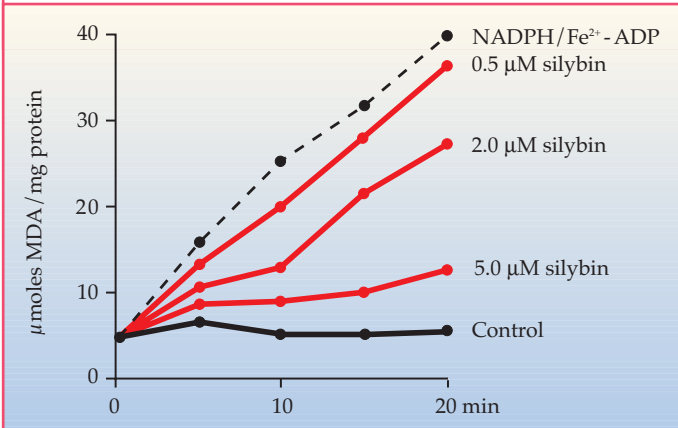


Fig. 7 Effects of single oral administration of SILIPHOS® (620 mg/kg as silybin) on the ESR spectra of 4-POBN-hydroxyethyl radical adducts detected in the bile of rats acutely treated with ethanol.

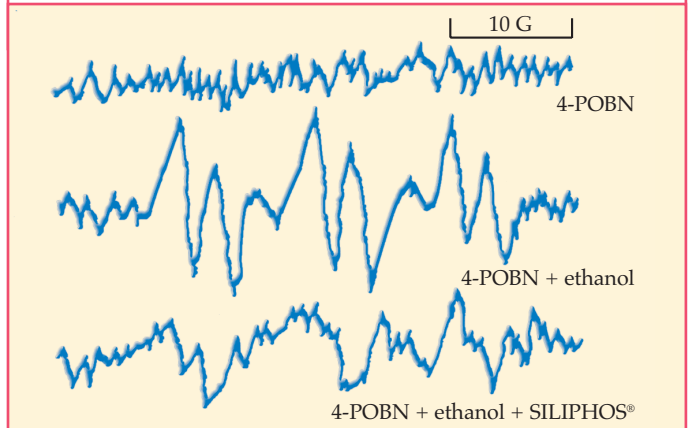
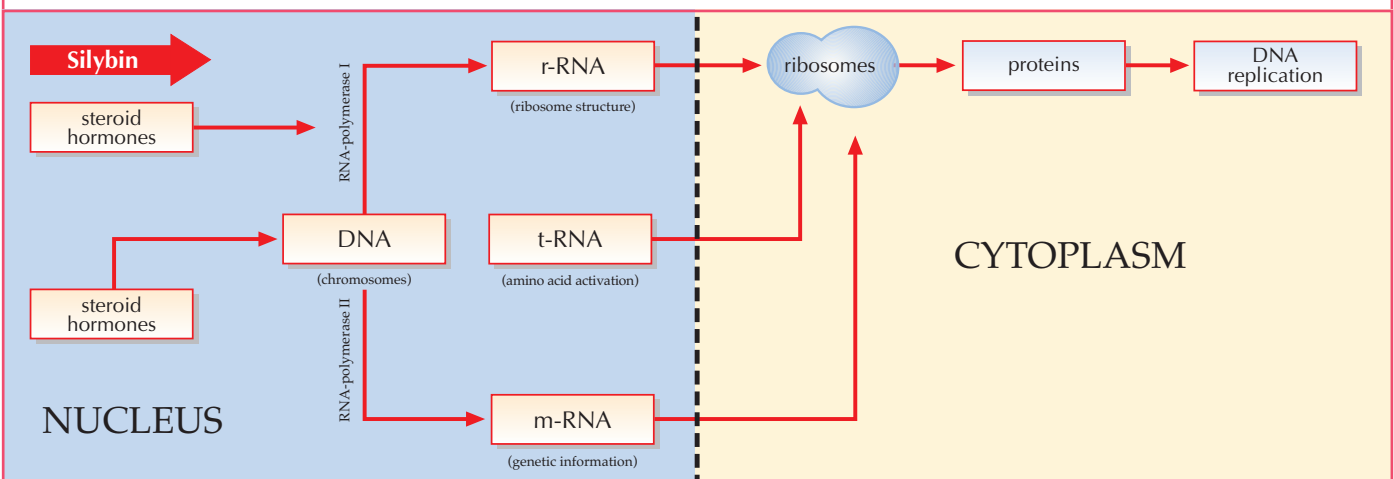


Fig. 8 Molecular mechanism for silybin stimulation of hepatic protein synthesis.



CLINICAL STUDIES

Pharmacological and toxicological results, added to those found from pharmacokinetic studies, have provided the basis for clinical testing of SILIPHOS®. Clinical studies, here reported, have been performed to evaluate the properties of this new complex in subjects with “pathological” impairment of liver function. The results, including the optimal tolerability obtained in these “extreme” clinical situations, give strong support for the use of SILIPHOS® in those “non pathological” conditions mostly associated with the action of damaging agents on liver cells. Vailati *et al.*¹⁸ performed an open randomized trial on 65 patients suffering from chronic persistent hepatitis. The protective effects of SILIPHOS® increased with the dose and

240 mg/die p.o. (as silybin) resulted to be the mean therapeutic dose whereas 360 mg/die p.o. (as silybin) was recommended for the treatment of the severe resistant form of hepatitis or during the initial management of the patients. In a study carried out on 232 patients with alcoholic, acute viral or iatrogen hepatitis, the subjects have been treated with 240 or 360 mg/die p.o. (as silybin) for 120 days. No side effects have been observed and SILIPHOS®, in comparison with placebo, showed its ability to improve liver condition.¹⁹ In a short-term pilot study performed on 20 patients with chronic active hepatitis, the biochemical parameters related to hepatocellular damage and necrosis were significantly reduced after 7 days of treatment with

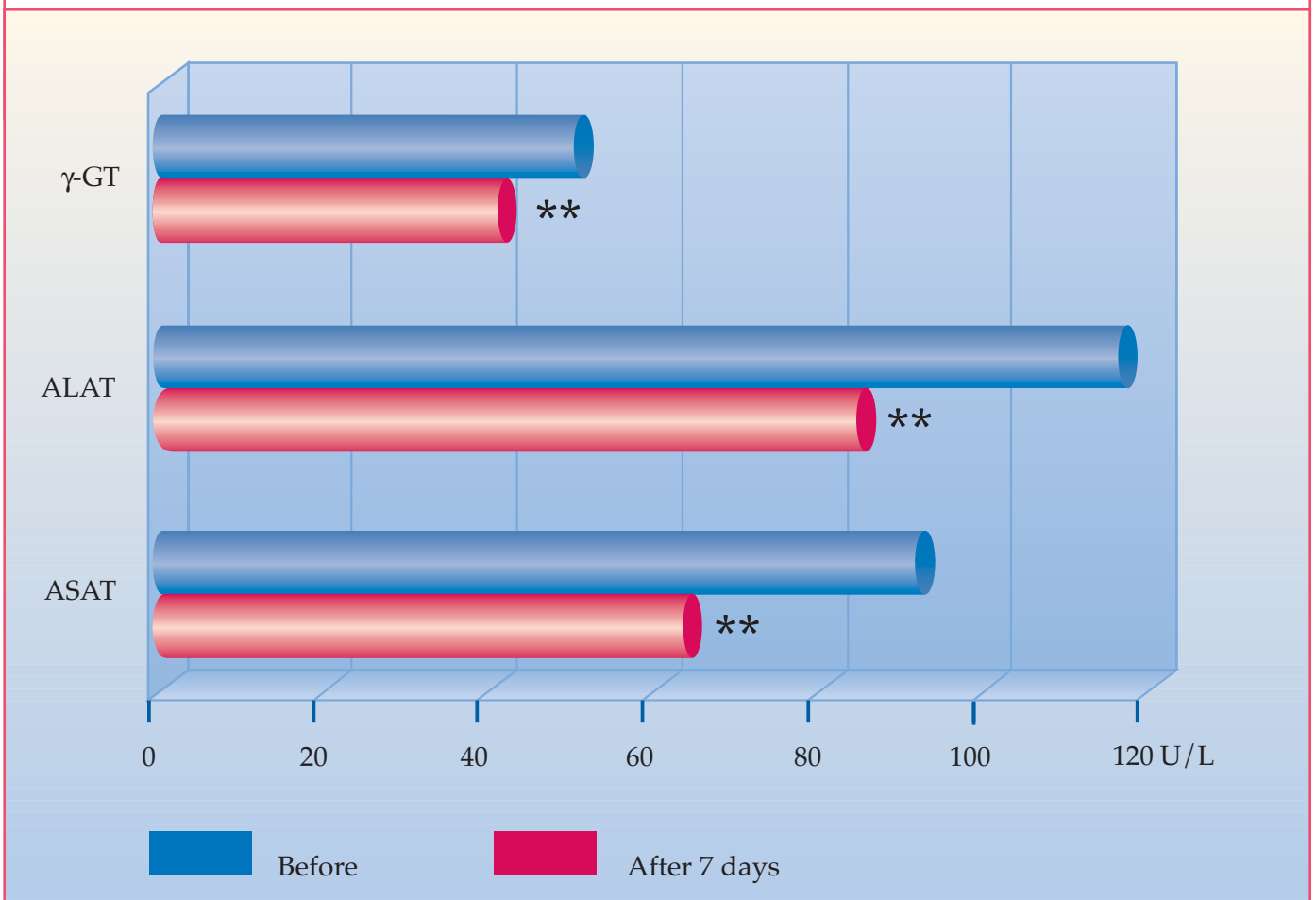
240 mg/die p.o. (as silybin) (Fig. 9).²⁰ Finally, a 2-month study on 8 patients complaining of chronic active hepatitis has shown the ability of SILIPHOS® to reduce serum MDA concentration and to increase galactose elimination by the liver.²¹

USAGE

Due to its ability to prevent liver damage of different etiology, SILIPHOS® represents a natural protector of the hepatocyte. Its use can be suggested in counteracting all situations in which oxidative stress can damage the hepatocellular functionality (ethanol, drugs, cellular aging, dietetic unbalance...).

SUGGESTED DAILY DOSES: 80-160 mg

Fig. 9 Effect of SILIPHOS® on hepatocellular damage measured as serum enzyme activity in patients with chronic active hepatitis.



REFERENCES

1. Schiff L., Schiff E.R., "Disease of the liver", V ed., J. B. Lippincott Co., Philadelphia, 1982.
2. Morazzoni P., Bombardelli E., *Fitoterapia* 50, 1 (1995).
3. Hahn G., Mayer A., *Osterr. Apoth.* 35, 849 (1981).
4. Hahn G., Lehmann H.D., Kurten M., Uebel H., Vogel G., *Arzneim. Forsch.* 18, 698 (1968).
5. Gabetta B., Zini G.F., Pifferi G., *Planta Med.* 55, 615 (1989).
6. *Drugs of the Future* 15, 226 (1990); *ibid.* 17, 248 (1992).
7. Morazzoni P., Magistretti M.J., Giachetti C., Zanolo G., *Eur. J. Drug Metabol. Pharmacokinet.* 17, 39 (1992).
8. Morazzoni P., Montalbetti A., Malandrino S., Pifferi G., *Eur. J. Drug Metabol. Pharmacokinet.* 18, 289 (1993).
9. Orlando R., Fragasso A., Lampertico M., Marena C., *Med. Sci. Res.* 19, 827 (1991).
10. Barzaghi N., Perucca E., Pifferi G., Crema A., *Flavonoids in Biology and Medicine*, Singapore, November 13-17, 1989.
11. Conti M., Malandrino S., Magistretti M.J., *Flavonoids in Biology and Medicine*, Singapore, November 13-17, 1989.
12. Conti M., Malandrino S., Magistretti M.J., *Jpn J. Pharmacol.* 60, 315 (1992).
13. Comoglio A., Leonarduzzi G., Carini R., Busolin D., Basaga H., Albano E., Tomasi A., Poli G., Morazzoni P., Magistretti M.J., *Free Rad. Res. Comm.* 11, 109 (1990).
14. Bosisio E., Benelli C., Pirola O., *Pharm. Res.* 25, 147 (1992).
15. Carini R., Comoglio A., Albano E., Poli G., *Biochem. Pharmacol.* 43, 2111 (1992).
16. Comoglio A., Tomasi A., Malandrino S., Poli G., Albano E., *Biochem. Pharmacol.* 50, 1313 (1995).
17. Sonnenbichler J., Zetl I., "Plants flavonoid in biology and medicine: biochemical, pharmacological and structure-activity Relationship". Alan R. Liss, Inc., N.Y., 1986.
18. Vailati A., Aristia L., Sozzè E., Milani F., Inglese V., Galenda P., Bossolo P.A., Ascari E., Lampertico M., Comis S., Marena G., *Fitoterapia* 64, 219 (1993).
19. Marena C., Lampertico M., *Planta Med.* 57, suppl., A124 (1991).
20. Buzzelli G., Moscarella S., Giusti A., Duchini A., Marena C., Lampertico M., *Int. J. Clin. Pharmacol. Ther. Toxicol.* 31, 456 (1993).
21. Moscarella S., Giusti A., Marra F., Marena C., Lampertico M., Relli P., Gentilini P., Buzzelli G., *Curr. Ther. Res.* 53, 98 (1993).

