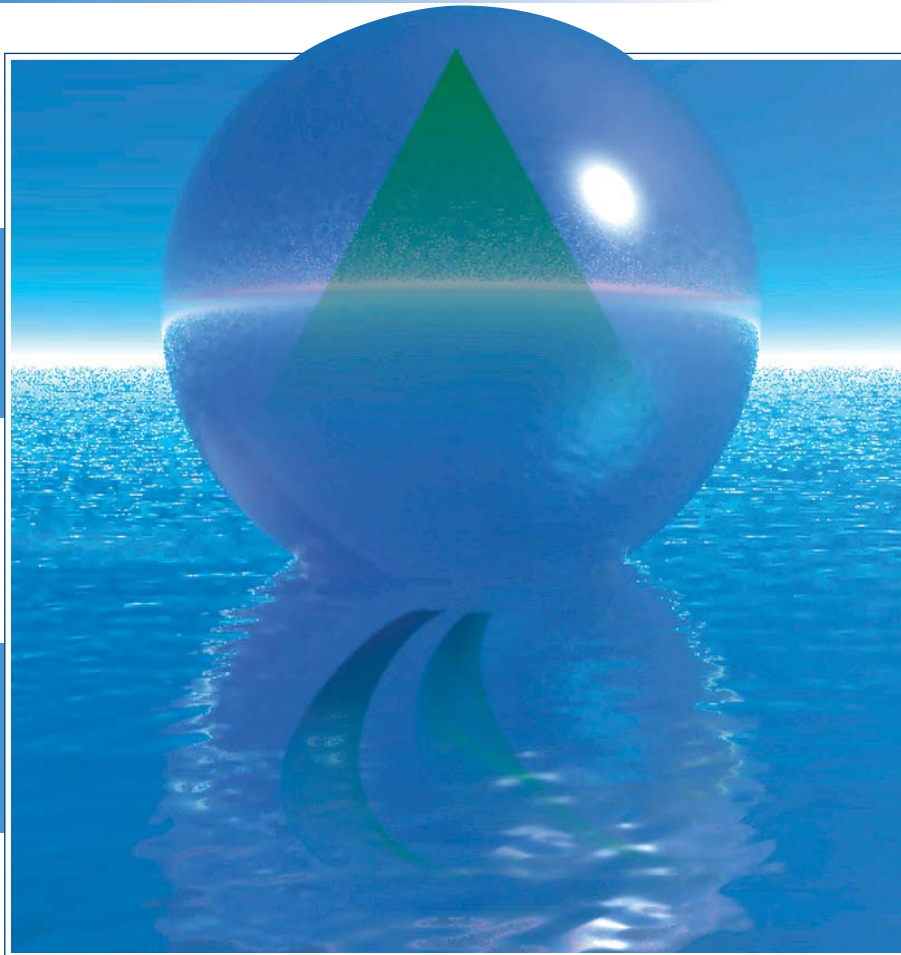
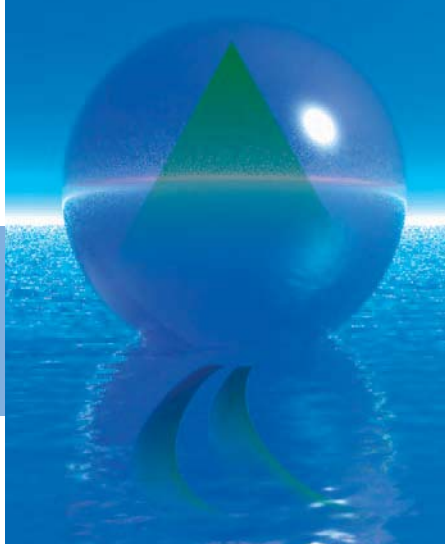


PHYTOSOME

INDENA'S PATENTED BIOAVAILABLE BOTANICAL DERIVATIVES





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.¹

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.² This is probably due to the removal of chemically related substances contributing with a synergic action to the activity of the main components.

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.

The hypothesis of an interaction with phospholipids, which are ubiquitous in plants and in animals, originated from a histochemical finding indicating that anthocyanosides from *Vaccinium myrtillus* L. show a strong affinity for specific cellular structures rich in phospholipids.³ Evidence that flavonoids as well as saponins and triterpenic acids, do form real complexes with phospholipids was obtained about ten years ago when these complexes could be prepared and chemically standardized.^{2,4-7}

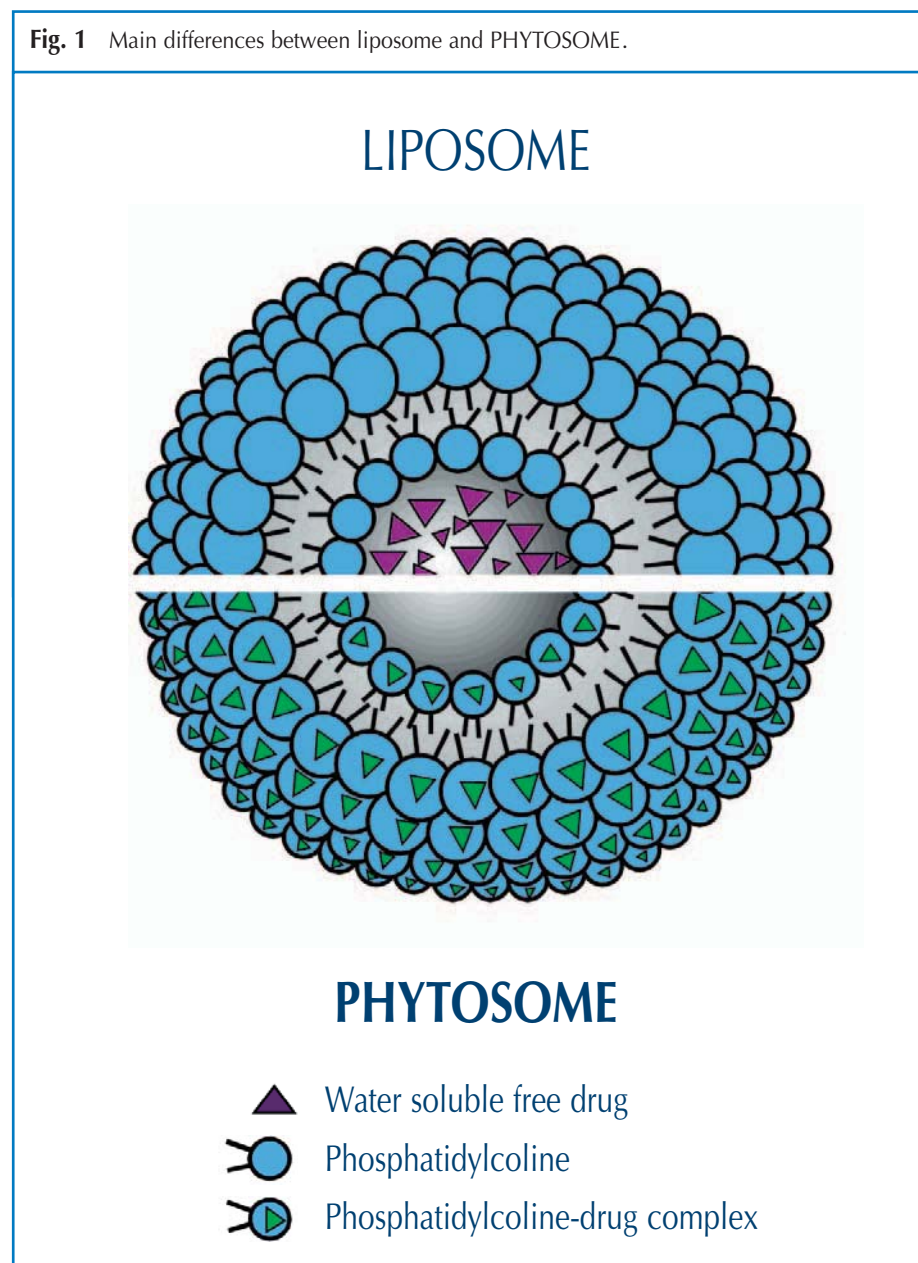
The complexes prepared by Indena

starting from pure active molecules or extracts containing them, topically or orally tested in pharmacodynamic tests, showed an increase in biological activity in comparison with the same compounds administered in free form at a equivalent dosage.^{2,4-12}

Pharmacokinetics studies demonstrated that the complexation with phospholipids substantially improves the bioavailability of some compounds.¹³⁻¹⁹

PHYTOSOME is the trade name of these patented lipophilic complexes²⁰⁻²³ produced by Indena.

Fig. 1 Main differences between liposome and PHYTOSOME.



PHYTOSOME CHEMICAL PROPERTIES

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.⁹ 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 (Fig. 1). In the case of the catechin-distearoylphosphatidylcholine 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 (Fig. 2, 3). The signals of the fatty chain are almost unchanged. Such evidences inferred that the two long aliphatics chains are wrapped around the active principle, producing a lipophilic envelope which shields the polar head of the phospholipid and the catechin. 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 (Fig. 4). 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.

Fig. 2 ¹³C-NMR spectrum of (+)-Catechin-distearoylphosphatidylcholine complex in comparison with those of its constituents.

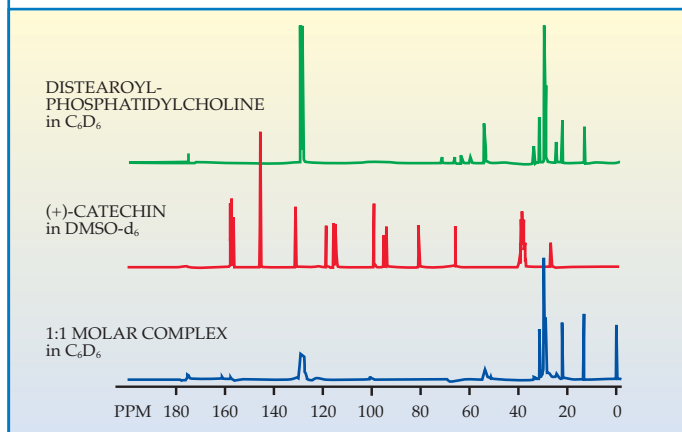


Fig. 3 ¹H-NMR spectrum of (+)-Catechin-distearoylphosphatidylcholine complex in comparison with those of its constituents.

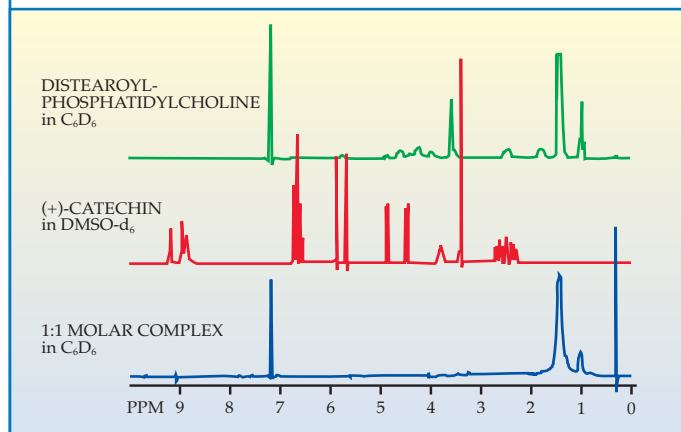
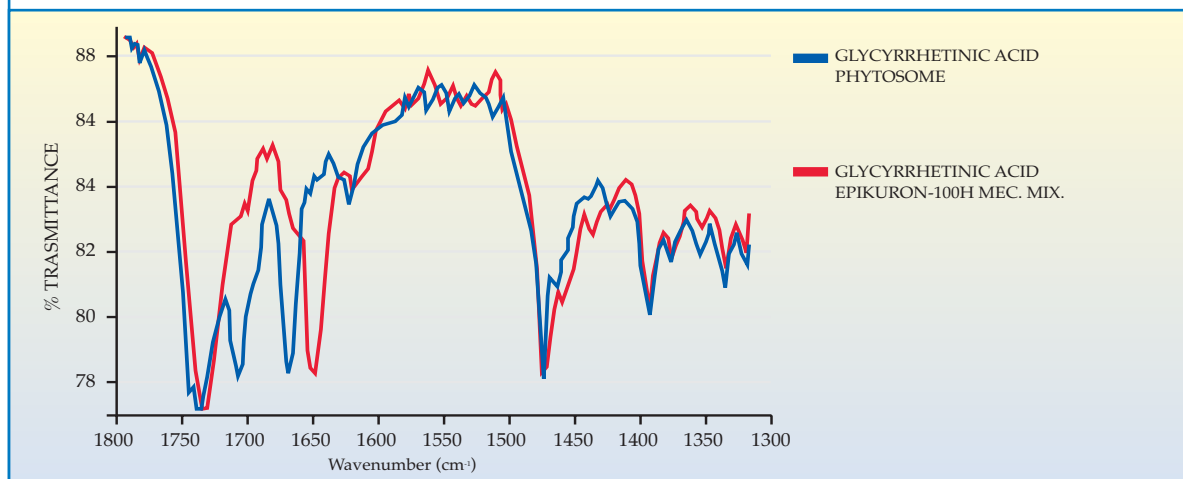


Fig. 4 FT-IR of glycyrrhetic acid complex with distearoylphosphatidylcholine and or their mechanical mixture.



PHYTOSOME BIOLOGICAL PROPERTIES

The increased bioavailability of the PHYTOSOME over the non complexed botanical derivatives has been demonstrated by pharmacokinetics studies¹³⁻¹⁹ or by pharmacodynamic tests in experimental animals^{12,24,25} and in human subjects.²⁶⁻³⁰



LEUCOSELECT® PHYTOSOME

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.



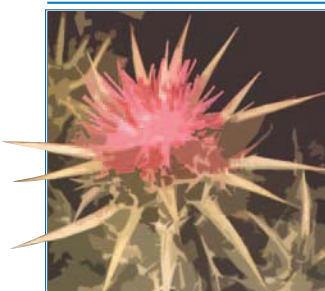
GINKGOSELECT® PHYTOSOME

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 makes it the ideal product even for long term treatments.



GREENSELECT® PHYTOSOME

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 demonstrated 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 improve their low and erratic oral bioavailability.



SILIPHOS®

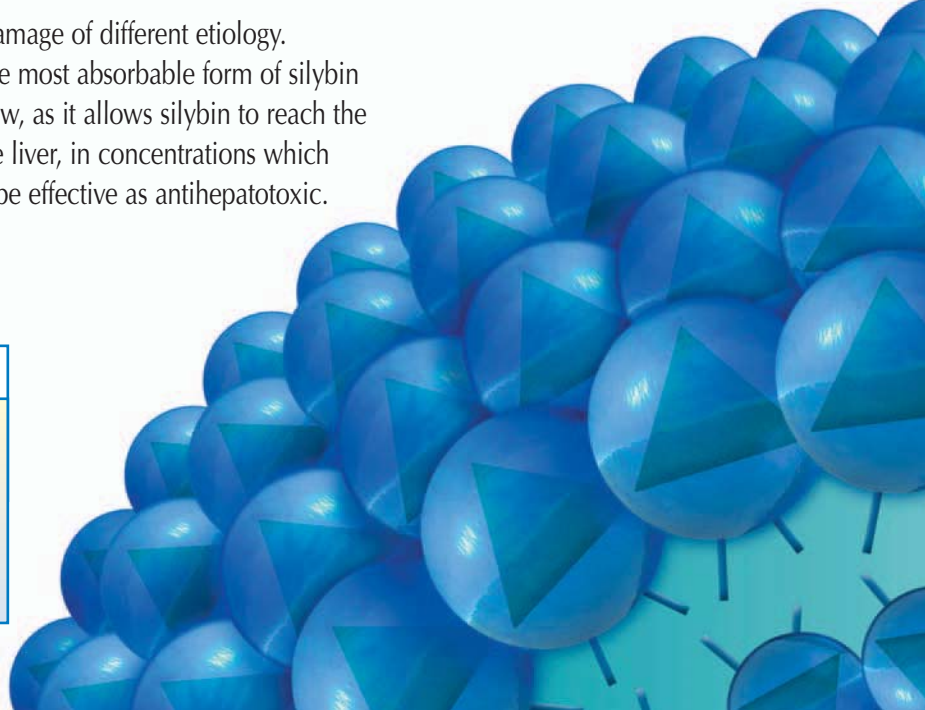
prevents liver damage of different etiology. SILIPHOS® is the most absorbable form of silybin known up to now, as it allows silybin to reach the target organ, the liver, in concentrations which are reported to be effective as antihepatotoxic.

Also available PHYTOSOMES

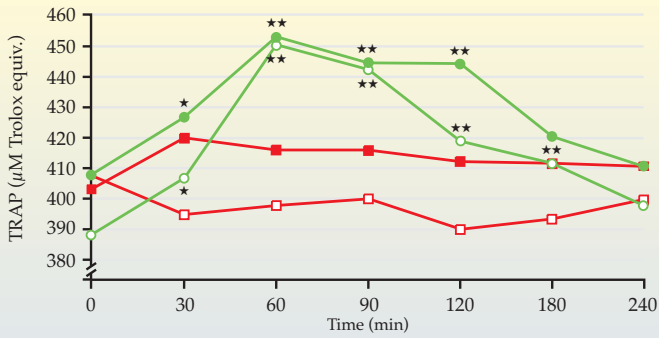
CENTELLA PHYTOSOME
(cicatrizing - trophodermic)

SILYMARIN PHYTOSOME
(antihepatotoxic)

GINSELECT® PHYTOSOME
(skin elasticity improver - adaptogenic)



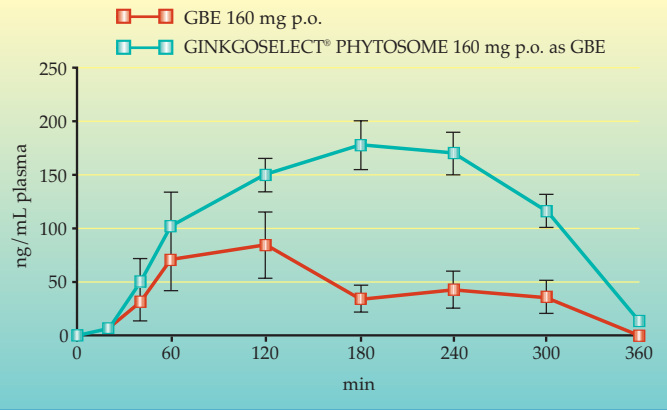
Effect of LEUCOSELECT® PHYTOSOME (300 mg/daily as LEUCOSELECT®) on total antioxidant capacity (trap) in healthy volunteers.



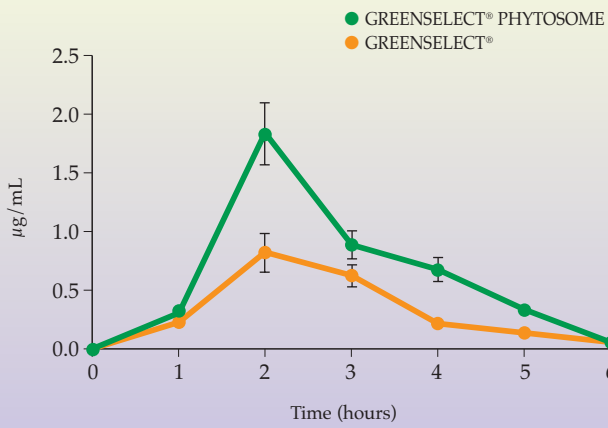
n=20 ★p <0.05 ★★p <0.01 vs basal values (0 min) - Split-plot ANOVA

□ Placebo - Day 1 ○ LEUCOSELECT® PHYTOSOME - Day 1
 ■ Placebo - Day 5 ● LEUCOSELECT® PHYTOSOME - Day 5

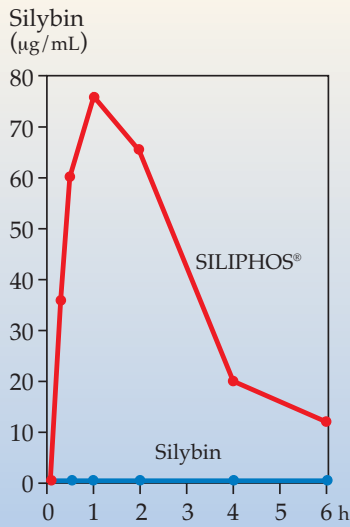
Plasma levels (LC-MS) of total ginkgolides (A and B) and bilobalide in healthy volunteers.



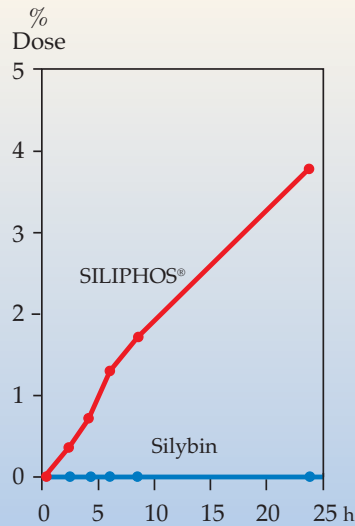
Time course of plasma EGCG after ingestion of GREENSELECT® and GREENSELECT® PHYTOSOME.



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



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



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